CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-356

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
BRAND NAME:	VIREAD®
GENERIC NAME:	Tenofovir Disoproxil Fumarate
DOSAGE FORM AND STRENGTH:	300 mg oral tablet
NDA:	21-356
TYPE:	Priority Review (1P)
APPLICANT:	Gilead Sciences, Inc.
SUBMISSION DATE:	May 1, 2001
OCPB DIVISION:	DPE III
ORM DIVISION:	DAVDP
OCPB Reviewer:	Jooran S. Kim, Pharm.D.
OCPB Team Leader:	Kellie S. Reynolds, Pharm.D.

I. Executive Summary

The applicant submitted NDA# 21-356 to seek approval for tenofovir disoproxil fumarate (tenofovir DF), an oral prodrug of the antiretroviral nucleotide analog tenofovir, for the treatment of HIV-1 infection. The proposed dosage regimen of tenofovir DF is 300 mg orally once daily.

A. Recommendations

The Clinical Pharmacology and Biopharmaceutics information provided by the applicant for NDA 21-356 is acceptable.

The applicant did not evaluate tenofovir DF in individuals with renal insufficiency. Because tenofovir DF is predominantly renally eliminated, the applicant should conduct a pharmacokinetic study in subjects with renal insufficiency as soon as possible, in order to provide adequate dosing recommendations in renal insufficiency.

The applicant did not conduct a mass balance study or determine plasma concentrations of tenofovir disproxil or mono-POC PMPA. The applicant should measure concentrations of tenofovir disoproxil and mono-POC PMPA in a pharmacokinetic study in order to determine relative amounts of these compounds compared to tenofovir in vivo.

The applicant did not determine specific active secretion pathways of tenofovir. The applicant should characterize the specific renal transport pathways of tenofovir in vivo (anionic vs. cationic transport). Once determined, the applicant should evaluate the potential for drug interactions between tenofovir DF and drugs that are renally eliminated and frequently used by the HIV population. Specific examples include: acyclovir, valacyclovir, ganciclovir, valganciclovir, cidofovir, cotrimoxazole, etc.

In the drug interaction study (Study 909), subjects were not instructed to take tenofovir DF with food in the tenofovir DF alone treatment of the LPV/RTV cohort. Increases in tenofovir concentrations may be a result of a food effect

when tenofovir DF was administered with LPV/RTV (which is taken with food). There is a safety concern that there may be a larger increase in tenofovir concentrations for patients taking higher doses of ritonavir with tenofovir DF. Another drug interaction study with LPV/RTV is recommended to determine the drug interaction potential between tenofovir DF and LPV/RTV under fed conditions, as appropriate. If these pharmacokinetic changes are confirmed, the applicant should conduct a drug interaction study between tenofovir DF 300 mg and ritonavir 400 mg to better characterize the drug interaction observed between tenofovir DF 300 mg and higher ritonavir doses.

B. Phase IV Commitments

1. The applicant should evaluate the pharmacokinetics of tenofovir DF in subjects with renal insufficiency as soon as possible, in order to provide adequate dosing recommendations for this population. This study should be analyzed and submitted within 6 months of approval.

2. The applicant should measure concentrations of tenofovir disoproxil and mono-POC PMPA in a pharmacokinetic study in order to determine relative amounts of these compounds compared to tenofovir in vivo.

3. The applicant should characterize the specific renal transport pathways of tenofovir in vivo (anionic vs. cationic transport). Once determined, the applicant should conduct in vivo studies that evaluate the potential for drug interactions between tenofovir DF and drugs that are renally eliminated and frequently used by the HIV population. Specific examples include: acyclovir, valacyclovir, ganciclovir, valganciclovir and cidofovir. All drugs should be administered as they are in the clinical setting with respect to food.

4. The applicant should go forward with their proposal to conduct additional drug interaction studies between tenofovir DF and enteric-coated didanosine, methadone, oral contraceptives and adefovir. All drugs should be administered as they are in the clinical setting with respect to food.

5. The applicant should conduct another drug interaction study between tenofovir DF and lopinavir/ritonavir to confirm lopinavir/ritonavir PK changes observed in Study 909. In this study, drugs should be administered appropriately with respect to food. If these pharmacokinetic changes are confirmed, the applicant should conduct a drug interaction study between tenofovir DF 300 mg and ritonavir 400 mg to better characterize the drug interaction observed between tenofovir DF 300 mg and higher ritonavir doses.

   All drug interaction studies should be analyzed and submitted within 18 months of approval.

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Tenofovir is a nucleotide analogue reverse transcriptase inhibitor active against HIV. The orally bioavailable prodrug, tenofovir disproxil fumarate (tenofovir DF), has been developed for the treatment of HIV infection. Tenofovir DF is cleaved by esterases for enhanced absorption. It is the first in new class of nucleotide analogs, whereas currently marketed related compounds are nucleoside analogs. Nucle**side** reverse transcriptase inhibitors are mono-, di-, and tri-phosphorylated to the moiety that inhibits HIV reverse transcriptase. Tenofovir, a nucle**otide** analogue, is already a monophosphate and, therefore, undergoes mono- and di-phosphorylation intracellularly to inhibit HIV reverse transcriptase.

The intended commercial formulation of tenofovir DF is 300 mg oral tablets. The clinical and intended commercial formulations are bioequivalent. The proposed dosage regimen is 300 mg orally once a day. Tenofovir DF and its metabolite have a prolonged intracellular half-life. Tenofovir has potent antiviral activity against wild-type strains of HIV-1. IC_{50} values range between 0.2-6.0μM. Tenofovir is also active against some multinucleoside-resistant HIV strains, in vitro.

Although the applicant did not conduct formal PK/PD studies to evaluate dose/exposure-response relationships, the 300 mg dose of tenofovir DF was selected for further study based on safety and efficacy results from Studies 901 and 902 conducted in HIV-infected individuals. Study 901 was a dose-ranging study (75 mg, 150 mg, 300 mg and 600 mg once daily) conducted for a duration of 15-35 days. There were limited PK data in the 75 mg and 150 mg dose groups and the time frame of this study was too short to comprehensively evaluate dose/exposure response relationships. In the short term, however, further HIV RNA reductions were not observed in the 600 mg dose group compared to tenofovir DF 300 mg once daily in Study 901.

Study 902 was a dose-comparison study also conducted in HIV-infected patients. This study evaluated the safety and efficacy of 75 mg, 150 mg and 300 mg once daily doses of tenofovir DF for a duration of 48 weeks. Tenofovir pharmacokinetics were not evaluated in this study. Tenofovir DF 300 mg once daily provided better efficacy than 75 mg or 150 mg dose groups, with acceptable safety margins. In both studies, decreases in HIV RNA were greater than 75 mg and 150 mg dose groups. Based on these results, tenofovir DF 300 mg once daily was chosen for Phase III trials.

In an earlier study (Study 701), two dose levels of intravenous tenofovir (1.0 mg/kg and 3.0 mg/kg) administered for 7 days of multiple dosing were evaluated in HIV-infected patients. In one week's time, HIV RNA reduction appeared to be related to dose. Like Study 901, however, the time frame of Study 701 was too short in duration to comprehensively determine dose/exposure response relationships with respect to safety and efficacy.

The oral bioavailability of tenofovir following administration of a 300 mg dose of tenofovir DF is approximately 25% in the fasted state, in a cross-study comparison. Following oral administration of tenofovir DF in the fasted state, tenofovir C_{max} was reached within 1.0 hour following dosing. C_{max} and AUC values following a tenofovir DF dose of 300 mg in fasted subjects are 296± 90 ng/mL and 2287± 685 ng*h/mL, respectively. Exposure is dose-proportional following single and multiple administrations

of tenofovir DF at doses ranging from 75 to 600 mg in HIV-infected adults. Administration of tenofovir DF 300 mg to healthy subjects resulted in similar pharmacokinetic profiles to those observed in patients.

Administration of tenofovir DF immediately following a high-fat meal increases the estimated tenofovir oral bioavailability by approximately 40%. C_{max} and AUC values are 326 ± 119 ng/mL and 3324± 1370 ng*h/mL following multiple doses of tenofovir DF 300 mg once daily in the fed state. Patients took tenofovir following a meal during clinical trials. The label will indicate patients should take tenofovir DF with a meal.

Volume of distribution at steady-state is 1.3± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg. An in vitro protein binding study indicated that tenofovir is less than 8% protein bound between concentrations of 0.01 to 25.01 µg/mL.

Tenofovir DF is a fumarate salt of tenofovir disoproxil that undergoes rapid enzymatic hydrolysis yielding tenofovir. In vitro, tenofovir DF is hydrolyzed rapidly ($T_{1/2}$ < five minutes) in human plasma, intestinal homogenate and liver homogenate. No metabolites of tenofovir were detected and there was no evidence of chiral inversion of [*R*]-tenofovir following in vitro experiments with rat liver microsomes.

Following T_{max}, tenofovir concentrations in serum decline in a biphasic manner with a terminal half-life ranging from 12 to 13 hours in HIV-infected patients and 18 to 19 hours in healthy subjects. This difference in half-life may be due to a shorter duration of blood sampling in HIV-infected patients (24 hours) compared to healthy volunteers (48 hours). Otherwise, all other pharmacokinetic parameters are comparable between the groups. In Study-99-701, 70 to 80% of the administered dose was recovered in the urine as unchanged tenofovir within 72 hours, following intravenous dosing. Tenofovir is eliminated by a combination of glomerular filtration and net tubular secretion as renal clearance exceeds estimated glomerular filtration rate. There may be competition with other compounds that rely extensively on active tubular secretion for excretion. There are no data indicating whether tenofovir is secreted by the anion or cation transporter.

The applicant conducted an in vitro study to evaluate the potential for tenofovir DF to inhibit CYP enzymes (CYP3A4, CYP2D6, CYP2C9, CYP2E1, and CYP1A) and one in vivo drug interaction study to evaluate the pharmacokinetic effects of tenofovir DF on lamivudine, didanosine, indinavir, lopinavir/ritonavir and efaverinz and vice versa.

In vitro, the prodrug tenofovir DF had no effect on the activity of any of the CYP450 enzymes, except for CYP1A, where a small (6%) but statistically significant reduction in the metabolism of 7-ethoxycoumarin was observed. Tenofovir did not inhibit the metabolism of any of the probe substrates. In vitro results indicate that the potential for clinically relevant drug-drug interactions due to inhibition of CYP enzymes following tenofovir DF administration is low.

To evaluate the potential for drug interactions in vivo, the applicant conducted a multiple-dose study investigating the pharmacokinetics of tenofovir disoproxil fumarate (TDF), lamivudine (3TC), didanosine (ddI), indinavir (IDV), lopinavir/ritonavir (LPV/RTV) and efavirenz (EFV) in healthy volunteers. Tables 1 and 2 summarize pharmacokinetic

effects of co-administered drug on tenofovir pharmacokinetics and effects of tenofovir on the pharmacokinetics of co-administered drug.

Table 4. Changes in pharmacokinetic parameters for tenofovir in the presence of the co-administered drug

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of VIREAD (mg)	n	Mean Ratio (with/without Co-administered Drug) of Tenofovir Pharmacokinetic Parameters (90% CI) No Effect = 1.00		
				C_{max}	AUC	C_{min}**
Lamivudine	150 twice daily x 7 days	300 once daily	15	1.02 (0.96, 1.08)	0.96 (0.85, 1.08)	0.92 (0.73, 1.12)
Didanosine*	250 or 400 once daily x 7 days	300 once daily	14	0.98 (0.86, 1.12)	0.94 (0.86, 1.02)	0.92 (0.79, 1.03)
Indinavir	800 three times daily x 7 days	300 once daily	13	1.14 (0.97, 1.33)	1.07 (0.95, 1.19)	1.06 (0.92, 1.21)
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	300 once daily	21	1.31 (1.12, 1.53)	1.34 (1.25, 1.44)	1.29 (1.11, 1.48)
Efaverinz	600 once daily x 14 days	300 once daily	29	1.07 (0.94, 1.22)	0.99 (0.92, 1.06)	1.00 (0.90, 1.11)

*Buffered formulation
** $C_{min}=C_{tau}$

Table 5. Changes in pharmacokinetic parameters for co-administered drug in the presence of tenofovir

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of VIREAD (mg)	n	Mean Ratio (with/without VIREAD) of Co-administered Drug Pharmacokinetic Parameters (90% CI) No Effect = 1.00		
				C_{max}	AUC	C_{min}**
Lamivudine	150 twice daily x 7 days	300 once daily	15	0.76 (0.66, 0.88)	0.97 (0.83, 1.15)	1.15 (1.08, 1.22)
Didanosine*	250 or 400 once daily x 7 days	300 once daily	14	1.28 (1.11, 1.48)	1.44 (1.31, 1.59)	- -
Indinavir	800 three times daily x 7 days	300 once daily	12	0.89 (0.70, 1.12)	0.95 (0.82, 1.10)	1.12 (0.96, 1.27)
Lopinavir	LPV/RTV 400/100 twice daily x 14 days	300 once daily	21	0.85 (0.77, 0.94)	0.85 (0.78, 0.93)	0.94 (0.85, 1.03)
Ritonavir	LPV/RTV 400/100 twice daily x 14 days	300 once daily	21	0.72 (0.57, 0.91)	0.76 (0.66, 0.87)	1.07 (0.78, 1.37)
Efaverinz	600 once daily x 14 days	300 once daily	30	0.96 (0.91, 1.02)	0.96 (0.93, 1.00)	0.97 (0.94, 0.99)

*Buffered formulation
** $C_{min}=C_{tau}$

Tenofovir pharmacokinetic parameters were not affected by the concomitant administration of 3TC, ddI or EFV. Tenofovir C_{max} increased by 14% with concomitant administration of IDV and tenofovir C_{max}, AUC and C_{min} increased by 31%, 34% and 29% with LPV/RTV. Subjects were not instructed to take tenofovir DF with food in the tenofovir DF alone treatment in the LPV/RTV cohort. These increases in tenofovir concentrations may be a result of a food effect when tenofovir DF was administered with LPV/RTV (taken with food). These tenofovir concentrations are similar to those observed in clinical trials and, therefore, the available safety data suggest these

concentrations are generally safe. Long term data are unavailable at this time. There is, however, a safety concern in that there may be a larger increase in tenofovir concentrations for patients taking higher doses of ritonavir with tenofovir DF. Another drug interaction study with LPV/RTV is recommended to determine the drug interaction potential between tenofovir DF and LPV/RTV under fed conditions, as appropriate.

A significant drug interaction was observed with ddI + TDF in which C_{max} and AUC values of ddI increased by 27% and 43%. A renal interaction is most likely the mechanism. Although the applicant did not observe ddI-associated adverse events (AEs) in pooled studies, the observed interaction and the monitoring of patients for potential for AEs that may be associated with ddI will be indicated in the label.

When tenofovir DF was administered with IDV, there was an 11% decrease in IDV C_{max}. This decrease is minimal and will not likely affect efficacy of IDV. Other IDV PK parameters were unchanged and comparable in variability.

Both C_{max} and AUC values of LPV were decreased by approximately 15% with concomitant administration of tenofovir DF. LPV C_{min} values of were unchanged. The decrease in C_{max} and AUC may be attributed to lower RTV concentrations. Concomitant administration of tenofovir with LPV/RTV decreased C_{max} and AUC values of RTV by 28% and 24%. Reasons for these decreases are unknown. The magnitude of these decreases is not enough to warrant a dosage adjustment of LPV/RTV at this time. Another drug interaction between tenofovir DF and LPV/RTV is recommended.

Based on in vitro and in vivo results, tenofovir DF is not hepatically metabolized and probably not affected by known Pgp inhibitors. It does not inhibit metabolism nor increase the clearance of CYP substrates. Tenofovir DF is not likely to affect known Pgp substrates. The potential exists for renal drug interactions between tenofovir DF and renally eliminated agents, considering the primary route of elimination of tenofovir is renal excretion, including active tubular secretion.

Age, sex or body weight did not have significant effects on the pharmacokinetics of tenofovir. There were insufficient data available from different racial and ethnic groups other than Caucasian to investigate potential pharmacokinetic differences between these groups. No data are available on the pharmacokinetics of tenofovir in pediatric or geriatric patients. Also, tenofovir DF has not been studied in patients with renal or hepatic insufficiency. No specific dosing recommendations will be included in the label for these special populations. The label will, however, include a warning regarding the expected effect of diminished renal function on tenofovir pharmacokinetics. Since tenofovir is not entirely renally eliminated, the label will also include a precaution for patients with hepatic insufficiency.

IV. Question-Based Review

A. General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Chemical name: 9-[2-(R)-[[bis[[(isopropoxycarbonyl)oxy]methoxy]-phosphinoyl] methoxy]propyl]adenine fumarate

Structure:

Molecular formula: $C_{23}H_{34}O_{14}N_5P$
Molecular weight: 635.52
Formulation: 300 mg oral tablet (contains 245 mg tenofovir disoproxil, or 135.6 mg-equivalents of tenofovir)

Composition:

	Clinical Formulation (in Study 902)		Commercial Formulation (in Study 907)	
Tablet Strength	75 mg		300 mg	
Tablet Shape	Round		Almond-Shaped	
Appearance	White to Off-White		Light Blue	
Dimension				
Ingredient	% w/w	mg/tablet	% w/w	mg/tablet
Tablet Core				
Tenofovir DF				300.00
Pregelatinized starch, NF				
Croscarmellose sodium, NF				
Lactose monohydrate, NF				
Microcrystalline cellulose, NF				
Magnesium stearate, NF				
Purified water, USP				
Film-Coating				
Opadry II Y-30-10671-A				
Purified Water, USP				

What is the proposed mechanism of drug action and therapeutic indication?

Tenofovir disoproxil fumarate, or tenofovir DF, is an oral prodrug of tenofovir. Once absorbed, the prodrug is cleaved by esterases. It is the first compound in a new class of nucleotide analog antiretrovirals developed for the treatment of HIV infection. Nucleo**side** reverse transcriptase inhibitors are mono-, di-, and tri-phosphorylated to the active moieties that inhibit HIV reverse transcriptase. Tenofovir, a nucle**otide** analogue, is already a monophosphate and, therefore, only undergoes mono- and di-phosphorylation intracellularly to inhibit HIV reverse transcriptase.

What is the proposed dosage and route of administration?

The proposed dosage regimen for tenofovir DF is 300 mg orally once a day.

What efficacy and safety information contributes to the assessment of clinical pharmacology and biopharmaceutics data?

Efficacy and safety information were collected in the following studies:

Pivotal clinical trials

Study 902: (n=189) Phase II, randomized, double-blind, placebo-controlled study. Patients were randomized to receive tenofovir DF 75 mg, 150 mg, 300 mg qd or placebo + background therapy. Duration of treatment: 48 weeks

Study 907: (n=552) Phase III, randomized, double-blind, placebo-controlled study. Subjects received tenofovir DF 300 mg qd or placebo + background regimen. At week 24, patients randomized to receive placebo were crossed over to receive open-label tenofovir 300 mg qd. Duration of treatment: 48 weeks

Safety data: There is nonclinical evidence of renal toxicity and bone abnormalities. Renal toxicity was evident in 4 animal species in which kidney changes were directly linked to tenofovir use. At this time, renal toxicity has not been shown in clinical trials. Three species exhibited bone abnormalities with tenofovir. Decreases in bone mineral densities (BMD) are thought by the Division to be caused by two possible mechanisms: renal tubular reabsorption defects secondary to tenofovir use or direct toxicity to cells involved in normal bone formation. Bone toxicity data were collected from Studies 902 and 907 (BMD, total alkaline phosphatase, calcium, phosphate and parathyroid hormone). Study 903 (for traditional approval) will provide additional longer term safety data.

Supportive clinical trials

Study 901: (n=59) Phase I/II, double-blind, placebo-controlled, dose-ranging, single-multiple-dose study. Patients were randomized to receive either tenofovir 75 mg qd, 75 mg qd + 500 mg bid hydroxyurea, 150 mg qd, 300 mg qd, 600 mg qd. Duration of treatment: 35 days (12 months extended dosing of tenofovir DF 300 mg qd)

Study 908: (n=291) Single-arm, open-label, compassionate access study. Patients

received background therapy + tenofovir DF 300 mg qd.

B. General Clinical Pharmacology

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Response endpoints for tenofovir DF are reduction in HIV RNA viral load, measured in copies/mL, and increase in CD4 cell counts, in clinical pharmacology and clinical studies. Specifically, HIV-RNA correlates with mortality and morbidity and CD4 cell counts indicate the status of the immune system. HIV-RNA is a validated surrogate endpoint. As HIV-RNA decreases, CD4 cell counts should increase.

The primary efficacy endpoint in the pivotal studies was the time-weighted change in $\log_{10}$ HIV RNA over 24 weeks.

Are the active moieties in serum appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the active moieties are appropriately identified and measured. Tenofovir DF is metabolized intracellularly to its active moiety, tenofovir diphosphate, via cellular kinases. Tenofovir is measured in serum to determine pharmacokinetic parameters. No other active metabolites have been identified.

The applicant originally used a reverse-phase ion-pair [redacted] assay for Studies 701 and 901, then used LC/MS/MS methods in Studies 907, 909 and 914 to better quantitate low concentrations of tenofovir (see Analytical Methods, Section F). Assays were validated and are acceptable.

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

- ***based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?***

The systemic exposures of tenofovir (C_{max} and AUC) were dose-proportional following single and multiple administrations of tenofovir DF at doses ranging from 75 to 600 mg in HIV-infected adults. Table 1 below summarizes the mean pharmacokinetic parameters of tenofovir. Figures 1a-c graphically compare tenofovir AUC, C_{max} and C_{min} values for tenofovir DF 75 mg, 150 mg, 300 mg and 600 mg at Day 15. Figure 2 illustrates mean tenofovir concentration-time curves for tenofovir DF 75 mg, 150 mg, 300 mg and 600 mg.

Table 1: Mean pharmacokinetic parameters (± SD) for tenofovir in serum and urine following administration of tenofovir DF 75 mg, 150 mg, 300 mg and 600 mg single- and multiple-dose once daily

Note: There was a 7-day washout between Days 1 (fasted) and 8 (fed)

Dose and Study Day	C_{max} (ng/mL)	AUC * (ng*h/mL)	C_{last} (ng/mL)	T_{max} (h)	$T_{½}$ (h)	CLcr (mL/hr/kg)	% dose in urine	CL/F (mL/hr/kg)
TDF 75 mg								
Day 1 (n=12)	68.6**	-	25.4**	0.8**	-	86 (16)	16 (9)	-
Day 8 (n=12)	68.2 (25.7)	365 (183)	21.5 (10.1)	1.8 (0.7)	-	82 (15)	27 (4)	-
Day 15 (n=12)	69.2 (19.4)	562 (261)	25.2 (10.7)	2.2 (1.1)	-	86 (15)	30 (10)	354**
TDF 150 mg								
Day 1 (n=7)	143.5 (71.1)	476 (251)	31.6 (4.7)	1.0 (0.5)	-	87 (17)	20 (9)	-
Day 8 (n=8)	148 (67.8)	896 (643)	38.5 (7.3)	2.4 (1.4)	-	88 (13)	23 (8)	-
Day 15 (n=8)	180.9 (69.1)	1572 (700)	38.7 (14.6)	2.1 (1.0)	12**	88 (18)	29 (11)	555**
TDF 300 mg								
Day 1 (n=8)	294.4 (137.2)	2093**	34.3 (7)	1.1 (0.7)	11.9**	94 (19)	19 (6)	910**
Day 8 (n=8)	362 (100.5)	3185 (866)	41.3 (12.4)	2.1 (1)	13 (4)	94 (11)	21 (6)	614 (176)
Day 15 (n=7)	325.5 (119.1)	3324 (1370)	64.4 (25.4)	2.7 (0.8)	12.9 (2.1)	99 (20)	32 (10)	588 (166)
Day 35 (n=6)	319 (108)	3299 (1070)	31.2 (4)	2.3 (1)	14.3 (1.1)	87 (27)	-	589 (171)
TDF 600 mg								
Day 1 (n=9)	611.5 (274.8)	3372**	61.7 (44.9)	0.9 (0.3)	13**	92 (23)	-	1083**
Day 8 (n=9)	611.8 (232.5)	5028 (1528)	62.7 (20.9)	1.4 (0.3)	12.7 (2.5)	96 (28)	13 (3)	734 (230)
Day 15 (n=9)	640.7 (191.9)	6068 (2468)	111.3 (53.2)	2.3 (0.8)	12.3 (1.5)	87 (22)	16 (3)	632 (191)
Day 35 (n=8)	550.8 (200.9)	5971 (2917)	53.1 (34.3)	2.2 (1)	15.3 (1.1)	92 (18)	17 (6)	631 (188)

* For the 75 mg and 150 mg cohorts, AUC=AUC $_{0\text{-last}}$
For Days 1 and 8, AUC=AUC $_{0-\infty}$
For Days 15 and 35, AUC=AUC $_{0\text{-}T}$
** Median values
- Not calculated due to missing data

Figures 1a-c: Tenofovir AUC $_{0\text{-}24}$ (ng*h/mL), C_{max} (ng/mL) and C_{min} (ng/mL) values for tenofovir DF 75 mg, 150 mg, 300 mg and 600 mg at Day 15

Figure 1a:

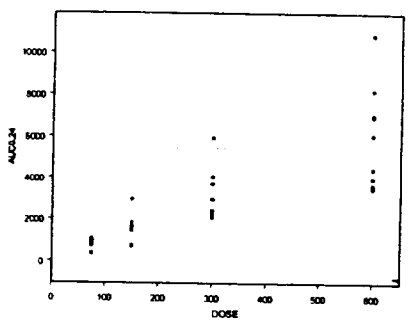

Figure 1b:

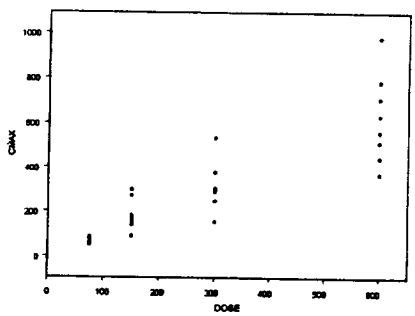

Figure 1c:

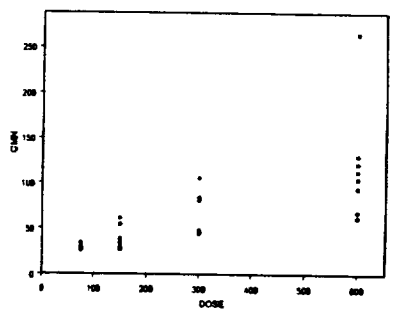

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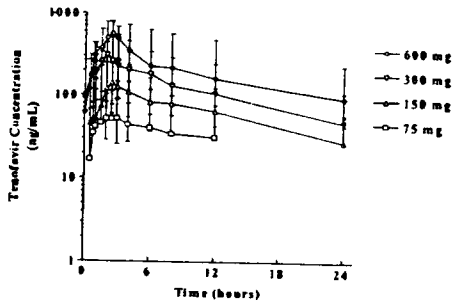
Figure 2: Steady-State Serum Tenofovir Concentration Versus Time Profile Following Administration of Tenofovir DF 300 mg with Food to HIV-Infected Patients (GS-97-901)



- ***how do PK parameters change with time following chronic dosing?***

Pharmacokinetic data for tenofovir following long term dosing (through 24 weeks to date) of tenofovir DF 300 mg are available in 7 HIV-infected adults (GS-99-907). Table 2 compares the pharmacokinetics of tenofovir in serum following the first dose and again following 12 and 24 weeks of once daily dosing.

Table 2: Mean pharmacokinetic parameters (± SD) for tenofovir in serum following administration of tenofovir DF 300 mg once daily at Day 1, Week 12 and Week 24

	C_{max} (ng/mL)	AUC* (ng*h/mL)	C_{min} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	CLcr (mL/hr/kg)	CL/F (mL/hr/kg)
Day 1 N=9	282 (139.2)	2929 (750)	46.2 (21.5)	2.4 (0.8)	12.1 (2.6)	97 (19)	660 (242)
Week 12 N=7	348.6 (121)	2968 (1156)	66.5 (37.6)	2.1 (0.8)	18.7 (13.5)	93 (19)	680 (322)
Week 24 N=7	256 (77)	2341 (491)	36.9 (16.8)	2.6 (1.0)	14.4 (4.6)	91 (21)	773 (270)

* For Day 1, AUC=$AUC_{0-\infty}$
For Weeks 12 and 24, AUC=AUC_{0-T}

The pharmacokinetics of tenofovir were not affected by long term dosing over 12 to 24 weeks. Tenofovir C_{max} and AUC_{ss} values on Week 24 were lower than those observed on Week 12, however these differences were not statistically significant. There were no alterations in calculated creatinine clearance from patients' pretreatment values over 24 weeks of study, indicating that once daily administration of tenofovir DF over 24 weeks did not adversely affect clinical estimates of renal function.

- **is the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

Although the applicant did not conduct formal PK/PD studies to evaluate exposure response relationships, there appears to be dose-response relationship favoring the 300 mg once daily dosing regimen based on HIV RNA decreases observed in Studies 901 and 902.

In the short-term dose-ranging study (Study 901), initial decreases in HIV RNA were greater in the 300 mg compared to the 75 mg and 150 mg groups. The 600 mg group did not exhibit further HIV RNA reductions. Subjects were dosed for 21 days. In Study 902, HIV RNA reductions were also greater in the 300 mg dose group compared to the 75 mg and 150 mg groups over 48 weeks. The 600 mg dosing regimen was not evaluated and pharmacokinetic data were not collected in Study 902.

How does the PK of tenofovir DF in healthy volunteers compare to that in patients? What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

There were no significant differences in the pharmacokinetics of tenofovir between HIV-infected patients (n = 17) and uninfected subjects (n = 36) ($p > 0.1538$) with the exception of terminal elimination half-life ($p < 0.0001$). This difference may be due to a shorter duration of blood sampling post-dose in HIV-infected patients vs. healthy subjects (24 hours vs. 48 hours, respectively). Variability was similar in both populations (%CV~25-40%). This variability is thought to be due to the cleaving of the prodrug and absorption of tenofovir.

Table 3: Pharmacokinetics of tenofovir following oral administration of 300 mg tenofovir DF administered in the fed State to females and males from Studies GS-97-901, GS-99-907 and GS-00-914

Parameter	Healthy Subjects	HIV-Infected Patients
N	36	17
$AUC_{0-\infty}$ (ng-hr/mL)	3096	2794
C_{max} (ng/mL)	327	317
T_{max} (hr)	2	2
T1/2 (hr)*	17	12

* $p < 0.0001$ Healthy vs. HIV-infected
Note: Median values

C. Intrinsic Factors and Special Populations

What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Are dosage adjustments recommended for any of these subgroups?

The applicant used a rank ANOVA model that included factors for HIV-infection, gender, age and weight, to assess the impact of demographic variables on tenofovir pharmacokinetics. Pooled single-dose data from studies GS-97-901, GS-99-907 and GS-00-914 were used.

a) ***body weight:*** There was no statistically significant effect of body weight on the pharmacokinetics of tenofovir.

b) ***gender:*** There were no significant differences in the pharmacokinetics of tenofovir between females and males, therefore, gender-specific dosage adjustment will not be indicated in the label.

c) ***race:*** There were insufficient data available from racial groups other than Caucasian to make any definitive conclusions regarding possible pharmacokinetic differences among these populations. Dosing recommendations for specific racial/ethnic groups will not be included in the label.

d) ***elderly:*** Since tenofovir DF is predominantly renally eliminated, the pharmacokinetics of tenofovir may be altered in the elderly due to diminished renal function. At this time, no data are available on the pharmacokinetics of tenofovir DF in individuals over 57 years of age. Specific dosage recommendations in this population will not be indicated in the label. The label will include a warning regarding the expected effect of diminished renal function on tenofovir pharmacokinetics.

e) ***pediatric patients:*** Tenofovir DF has not been evaluated in patients less than 18 years of age. A study of tenofovir DF in pediatric patients (2 to 18 years) is currently being developed.

f) ***hepatic impairment:*** No data are available on the pharmacokinetics of tenofovir DF in patients with hepatic impairment. Tenofovir exposure may not be affected in individuals with hepatic insufficiency since tenofovir is primarily eliminated through the kidneys. However, because tenofovir is not entirely renally excreted (70-80%), tenofovir concentrations may increase in pateints with hepatic insufficiency. Thus, because there are not sufficient safety data at doses higher than 300 mg qd, a hepatic insufficiency study may be useful. The applicant plans to conduct a study evaluating tenofovir DF in this population.

d) ***renal impairment:*** No data are available on the pharmacokinetics and safety of tenofovir in patients with CrCl < 60 mL/min. A study of tenofovir DF in subjects with varying degrees of renal insufficiency, including end-stage renal disease, is currently under development (Study GS-01-919). This protocol has not yet been submitted to the Agency. At this time, specific dosing recommendations will not be included in the label for this population. The label will include a warning regarding the expected effect of diminished renal function on tenofovir pharmacokinetics.

h) ***pregnancy or lactation:*** There is no information regarding the use of tenofovir DF in pregnant or lactating women.

D. Extrinsic Factors

What extrinsic factors (drugs, herbals, diet, smoking, alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

To date, the sponsor has evaluated the effects of specific drugs (see Drug-drug interactions) and food (see Biopharmaceutics) on the pharmacokinetics of tenofovir. The applicant also evaluated the metabolic stability of tenofovir DF and tenofovir and determined that neither compound is a substrate of CYP enzymes. It was also determined that the inhibitory potential of tenofovir DF and tenofovir on CYP3A4, CYP2D6, CYP2C9, CYP2E1, and CYP1A enzymes is low.

Drug-Drug Interactions

a) is there an in vitro basis to suspect in vivo drug-drug interactions? Is the drug a substrate of CYP enzymes? is the drug an inhibitor and/or an inducer of CYP

enzymes?

Tenofovir DF undergoes rapid enzymatic hydrolysis yielding tenofovir. In vitro, tenofovir DF was hydrolyzed rapidly ($T_{1/2}$ < five minutes) in human plasma, intestinal homogenate and liver homogenate.

To assess the metabolic stability of tenofovir, radiolabeled drug was studied in human plasma and in homogenates of human liver and intestine. The stability of tenofovir was also examined in liver microsomes obtained from animals, including rats following induction of hepatic metabolizing enzymes with [redacted]. In these in vitro assessments, no metabolites of tenofovir were detected with or without the addition of cofactors required for metabolism. Additionally, there was no evidence of chiral inversion of tenofovir during incubation.

The applicant conducted an in vitro study using human hepatic microsomes to evaluate the inhibitory potential of tenofovir DF on CYP enzymes (CYP3A4, CYP2D6, CYP2C9, CYP2E1, and CYP1A). The prodrug tenofovir DF had minimal or no effect on the activity of any of the CYP450 isoforms. Tenofovir itself did not inhibit the metabolism of any of the probe substrates. These results indicate that the inhibitory potential of tenofovir DF on drugs metabolized by CYP enzymes is low.

b) is the drug a substrate and/or an inhibitor of PGP transport processes or other metabolic/transporter pathways that may be important?

Although the applicant did not formally evaluate whether tenofovir DF is a substrate, inducer or inhibitor of p-glycoprotein (Pgp) or other metabolic/transporter pathways using specific probes, the drug interaction study indicates that the possibility of a significant interaction between tenofovir and Pgp occurring is minimal, in vivo (IDV and RTV are Pgp substrates and inhibitors).

c) what other co-medications are likely to be administered to the target patient population?

Likely co-medications in the HIV population are: other antiretrovirals, medications for the treatment of opportunistic infections, HMG Co-A reductase inhibitors and methadone. To date, the applicant has conducted drug interaction studies with lamivudine, didanosine, indinavir, lopinavir/ritonavir and efaverinz. The applicant plans to conduct future drug interaction studies with oral contraceptives, enteric-coated didanosine, adefovir and methadone.

Unresolved drug interactions still remain, particularly with drugs that are renally eliminated. Some examples include: acyclovir, valacyclovir, ganciclovir, valganciclovir and cotrimoxazole.

d) are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

The sponsor conducted one study investigating the pharmacokinetics of tenofovir disoproxil fumarate (TDF), lamivudine (3TC), didanosine (ddI), indinavir (IDV),

lopinavir/ritonavir (LPV/RTV) and efavirenz (EFV) in healthy volunteers. Data are summarized in Tables 4 and 5.

Tenofovir pharmacokinetic parameters were not affected by the concomitant administration of 3TC, ddI or EFV. Tenofovir C_{max} increased by 14% with concomitant administration of IDV and tenofovir C_{max}, AUC and C_{min} increased by 31%, 34% and 29% with LPV/RTV. Subjects were not instructed to take tenofovir DF with food in the tenofovir DF alone treatment of the LPV/RTV cohort. These increases in tenofovir concentrations may be a result of a food effect when tenofovir DF was administered with LPV/RTV, which is taken with food. These tenofovir concentrations are similar to those observed in clinical trials and, therefore, the available safety data suggest these concentrations are generally safe. Long term data are unavailable at this time. There is, however, a safety concern that there may be a larger increase in tenofovir concentrations for patients taking higher doses of ritonavir with tenofovir DF. Another drug interaction study with LPV/RTV is recommended to determine the drug interaction potential between tenofovir DF and LPV/RTV under fed conditions, as appropriate.

C_{max} values of 3TC were decreased when given with tenofovir. Least-squares mean ratios for 3TC in combination with TDF was 76% (90%CI=66%-88%) for C_{max} and 97.3% (90%CI=82%-115%) for AUC. Overall exposure of 3TC did not appear to change, however, a decrease in 3TC C_{max} was observed. Because the mechanism of action of 3TC is intracellular and the total exposure of 3TC did not change with TDF, the efficacy of 3TC is most likely unaffected by this decrease in C_{max}. Dosage adjustments are not recommended at this time.

A significant drug interaction was observed with didanosine + tenofovir DF in which C_{max} and AUC values of didanosine increased by 28% and 44%. A renal interaction is the most likely the mechanism. Although the applicant did not observe ddI-associated AEs in pooled studies, patients should be warned of this possible drug interaction and potential for AEs that may be associated with ddI.

When tenofovir DF was administered with IDV, there was an 11% decrease in IDV C_{max}. This decrease is minimal and will not likely affect efficacy of IDV. Other IDV PK parameters were unchanged and comparable in variability.

Both C_{max} and AUC values of LPV were decreased by approximately 15% with concomitant administration of tenofovir DF. LPV C_{min} values of were unchanged. The decrease in C_{max} and AUC may be attributed to lower RTV concentrations. Concomitant administration of tenofovir with LPV/RTV decreased C_{max} and AUC values of RTV by 28% and 24%. Reasons for these decreases are unknown. The magnitude of these decreases is not enough to warrant a dosage adjustment of LPV/RTV at this time.

Efaverinz PK parameters were not affected by tenofovir DF.

Table 4. Changes in pharmacokinetic parameters for tenofovir in the presence of the co-administered drug

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of VIREAD (mg)	n	Mean Ratio (with/without Co-administered Drug) of Tenofovir Pharmacokinetic Parameters (90% CI) No Effect = 1.00		
				C_{max}	AUC	C_{min}**
Lamivudine	150 twice daily x 7 days	300 once daily	15	1.02 (0.96, 1.08)	0.96 (0.85, 1.08)	0.92 (0.73, 1.12)
Didanosine*	250 or 400 once daily x 7 days	300 once daily	14	0.98 (0.86, 1.12)	0.94 (0.86, 1.02)	0.92 (0.79, 1.03)
Indinavir	800 three times daily x 7 days	300 once daily	13	1.14 (0.97, 1.33)	1.07 (0.95, 1.19)	1.06 (0.92, 1.21)
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	300 once daily	21	1.31 (1.12, 1.53)	1.34 (1.25, 1.44)	1.29 (1.11, 1.48)
Efaverinz	600 once daily x 14 days	300 once daily	29	1.07 (0.94, 1.22)	0.99 (0.92, 1.06)	1.00 (0.90, 1.11)

*Buffered formulation
** $C_{min}=C_{tau}$

Table 5. Changes in pharmacokinetic parameters for co-administered drug in the presence of tenofovir

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of VIREAD (mg)	n	Mean Ratio (with/without VIREAD) of Co-administered Drug Pharmacokinetic Parameters (90% CI) No Effect = 1.00		
				C_{max}	AUC	C_{min}**
Lamivudine	150 twice daily x 7 days	300 once daily	15	0.76 (0.66, 0.88)	0.97 (0.83, 1.15)	1.15 (1.08, 1.22)
Didanosine*	250 or 400 once daily x 7 days	300 once daily	14	1.28 (1.11, 1.48)	1.44 (1.31, 1.59)	- -
Indinavir	800 three times daily x 7 days	300 once daily	12	0.89 (0.70, 1.12)	0.95 (0.82, 1.10)	1.12 (0.96, 1.27)
Lopinavir	LPV/RTV 400/100 twice daily x 14 days	300 once daily	21	0.85 (0.77, 0.94)	0.85 (0.78, 0.93)	0.94 (0.85, 1.03)
Ritonavir	LPV/RTV 400/100 twice daily x 14 days	300 once daily	21	0.72 (0.57, 0.91)	0.76 (0.66, 0.87)	1.07 (0.78, 1.37)
Efaverinz	600 once daily x 14 days	300 once daily	30	0.96 (0.91, 1.02)	0.96 (0.93, 1.00)	0.97 (0.94, 0.99)

*Buffered formulation
** $C_{min}=C_{tau}$

e) are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

In vitro, the applicant has conducted metabolism, CYP inhibition and protein binding studies for tenofovir DF. At this time, there are no unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding.

In short, it is concluded that tenofovir DF is not metabolized by CYP enzymes and not affected by known Pgp inhibitors. It does not inhibit metabolism or increase the clearance of CYP substrates. Tenofovir DF most likely does not affect known Pgp

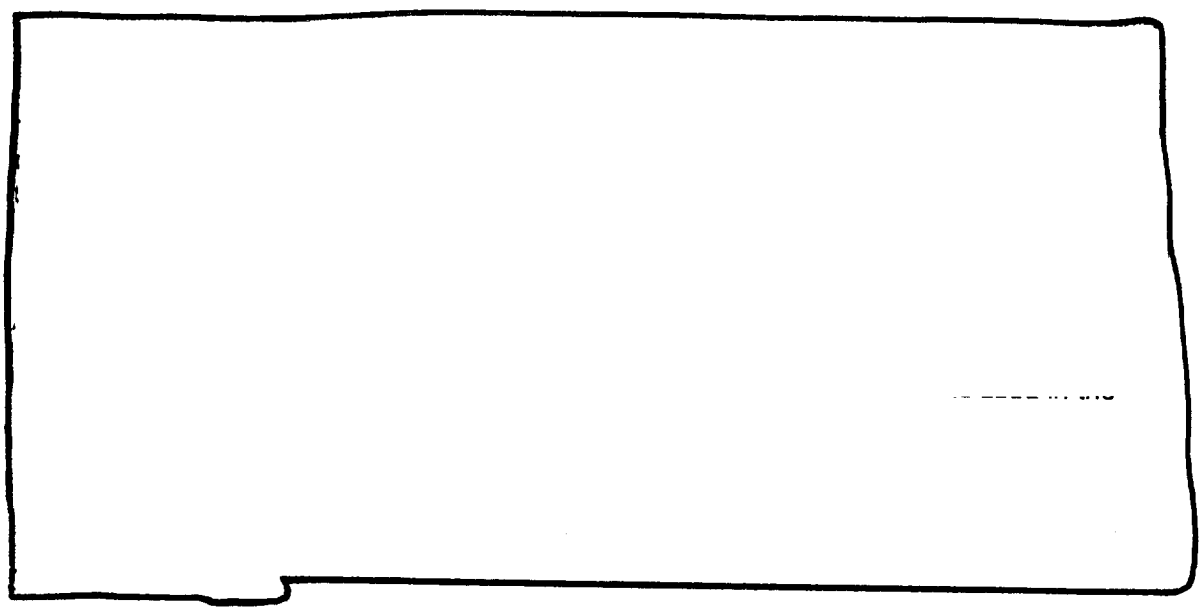
substrates. Because of its renal elimination pathway, tenofovir DF may affect renally eliminated drugs.

What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?

Tenofovir DF is mainly eliminated through the kidneys with approximately 70-80% of absorbed drug being recovered in urine. The applicant did not conduct a study evaluating how the pharmacokinetics of tenofovir DF differ in individuals with renal insufficiency, therefore, specific dosing recommendations for tenofovir DF in this subpopulation cannot be made at this time. According to the applicant, a renal insufficiency study is currently under development. The label will include a warning regarding the expected effect of diminished renal function on tenofovir pharmacokinetics.

Since the applicant has not conducted a mass balance study of tenofovir DF, the fate of the 20-30% of drug is unknown. The applicant will, therefore, conduct a hepatic insufficiency study to better characterize dosing adjustments that may be necessary in these patients.

E. General Biopharmaceutics



What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

Of pivotal clinical trials, the clinical formulation was used in Study GS-99-902 and the intended commercial formulation in Study GS-99-907. Study GS-00-914 evaluated the bioequivalence of the intended commercial formulation (1 x 300 mg tablet) to the clinical formulation (4 x 75 mg oral tablet). The intended commercial formulation is bioequivalent to the clinical formulation as 90%CI values for Cmax and AUC fall within 80-125% limits, summarized in Table 6.

Table 6. Mean pharmacokinetic parameters (SD), 90%CI values and % mean ratios for the clinical formulation vs. intended commercial formulation of tenofovir DF

	C_{max} (ng/mL)	AUC (ng*h/mL)	T_{max} (h)	% dose recovered in urine	CLr (mL/hr/kg)
(Ref) Clinical formulation 4 x 75 mg tablets (fasted)	307 (89)	2266 (550)	1.01 (0.60)	16.9 (4.9)	172.5 (67)
(Test) Commercial formulation 1 x 300 mg tablet (fasted)	296 (90)	2287 (685)	0.99 (0.38)	16.7 (4.8)	167.3 (44)
90%CI	**87.8-105.6**	**95.8-105.8**			
% mean ratio	**96.3**	**100.7**			

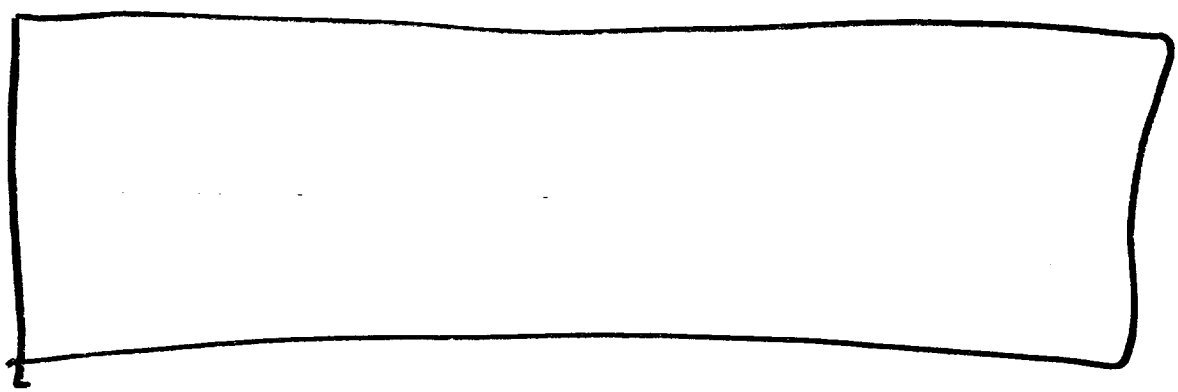
What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

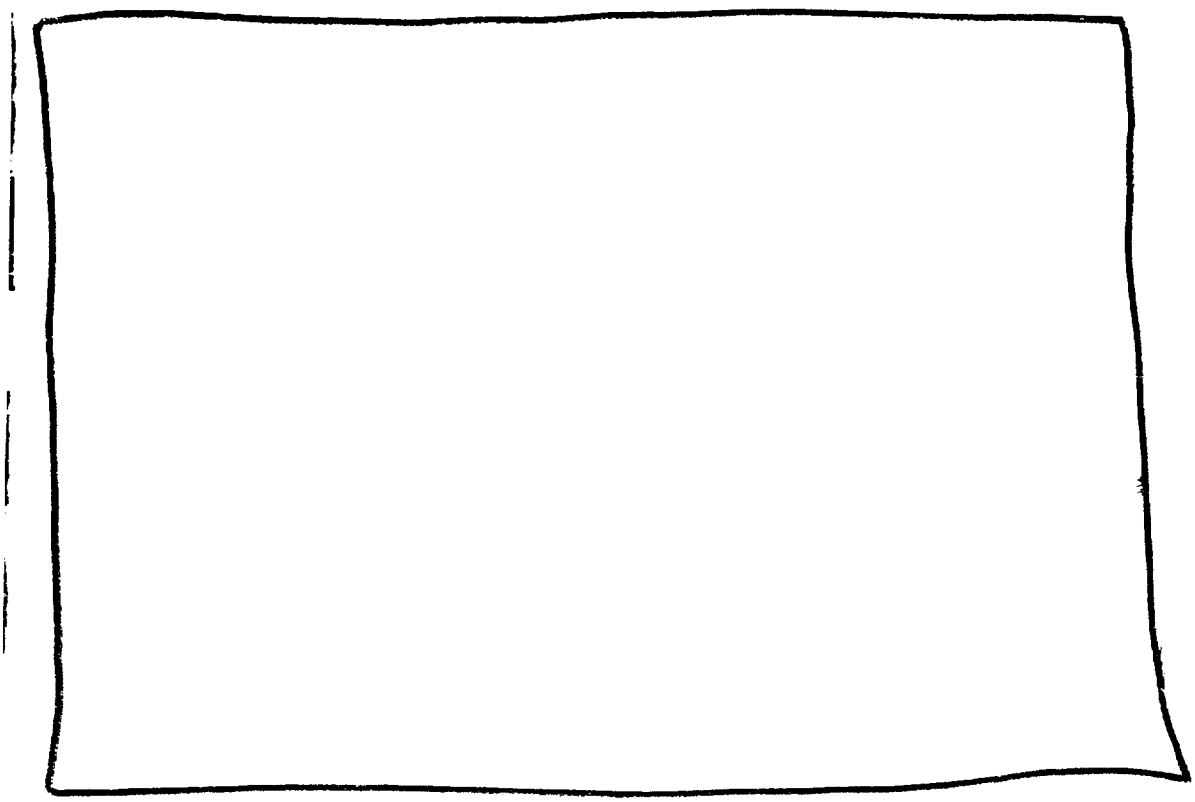
In Study GS-00-914, consumption of a high-fat breakfast prior to the administration of tenofovir DF 300 mg resulted in a significant increase in bioavailability. Geometric mean AUC and Cmax values were approximately 40% and 14% higher under fed conditions. Tmax was also delayed by one hour, resulting in Tmax at 2 hours. The label will indicate that tenofovir DF should be taken following a meal, as stated in clinical efficacy trials.

Table 7. Mean pharmacokinetic parameters (SD), 90%CI values and % mean ratios for fasted vs. fed conditions of the intended commercial formulation of tenofovir DF

	C_{max} (ng/mL)	AUC (ng*h/mL)	T_{max} (h)	% dose recovered in urine	CLr (mL/hr/kg)
(Ref) Commercial formulation 1 x 300 mg TDF (fasted)	296 (90)	2287 (685)	0.99 (0.38)	16.7(4.8)	167.3 (43.8)
(Test) Commercial formulation 1 x 300 mg TDF (fed)	334 (80)	3100 (598)	2.03 (0.88)	23.5 (4.9)	168.6 (41.1)
90%CI	**104.4-125.4**	**131.5-145.1**			
% mean ratio	**114.4**	**138.2**			

F. Analytical Methods





Signed:

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Concurrence:

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5 page(s) of revised draft labeling has been redacted from this portion of the review.

VI. Appendices (Filing Form and Individual Study Reviews)

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-356	Brand Name	VIREAD
OCPB Division (I, II, III)	III	Generic Name	Tenofovir disoproxil fumarate
Medical Division	Antivirals (HFD-530)	Drug Class	Nucleotide analogue
OCPB Reviewer	Jooran S. Kim, Pharm.D.	Indication(s)	Treatment of HIV infection in adults
OCPB Team Leader	Kellie S. Reynolds, Pharm.D.	Dosage Form	300 mg tablets
		Dosing Regimen	300 mg qd
Date of Submission	May 1, 2001	Route of Administration	PO
Estimated Due Date of OCPB Review	Sept. 27, 2001	Sponsor	Gilead Sciences Inc.
PDUFA Due Date	Nov. 1, 2001	Priority Classification	P
Division Due Date	Oct. 22, 2001		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X	1 study	1 study	
Blood/plasma ratio:				
Plasma protein binding:	X	1 study	1 study	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
I. Patients-				
single dose:	X	GS-96-701 GS-97-901	2 studies	
multiple dose:	X	GS-96-701 GS-97-901 GS-99-907	3 studies	
Dose proportionality -				
fasting / non-fasting single dose:	X	GS-97-901	1 study	
fasting / non-fasting multiple dose:	X	GS-96-701 GS-97-901	2 studies	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	GS-00-909	1 study	
In-vivo effects of primary drug:	X	GS-00-909	1 study	
In-vitro:	X	1 study	1 study	
Subpopulation studies -				
ethnicity:				
gender:	X	GS-97-901 GS-99-907 GS-00-914	3 studies	
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:	X	GS-96-701	1 study	
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:	X	GS-00-914	1 study	
replicate design; single / multi dose:				
Food-drug interaction studies:	X	GS-00-914	1 study	
Dissolution:	X	1 study	1 study	Data requested
(IVIVC):				
Bio-wavier request based on BCS				
BCS class	X	1 study	1 study	Data requested
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies	[redacted]	10	10	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Comments have been sent to applicant for data requests.
QBR questions (key issues to be considered)		**What are the main clinical trials (pivotal and supportive) for NDA 21-356?** **What is the indication for tenofovir and the proposed dosage regimen?** **Has the sponsor used the intended formulations in the pivotal clinical trials? If not, is the clinical formulation bioequivalent to the intended market formulation?** **What is the sponsor's rationale for selection of dose?** **Is there a food-effect with tenofovir?** **What are the drug-drug interactions with tenofovir? What are the PK differences observed with these drug-drug interactions and are they clinically significant?** **Does an exposure-response relationship exist for tenofovir in the treatment of HIV?** **Do PK/PD parameters differ between different racial/ethnic groups?** **Do PK/PD parameters differ in the pediatric population?** **Do PK/PD parameters differ in the geriatric population?** **Has the sponsor identified any genotypic/phenotypic differences in drug metabolism?** **Are there sex/gender differences with tenofovir?** **Does renal impairment alter the pharmacokinetics of tenofovir?** **Does hepatic impairment alter the pharmacokinetics of tenofovir?** **Note: Listed are general questions. Specific QBR questions are in the CPB review as per GRP.**

Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

In vitro metabolism of 14C-PMPA in human and animal tissues
Volume 2.061

OBJECTIVES:

1) To evaluate the in vitro metabolism of 14C-PMPA in normal and [redacted] induced rat liver microsomes;
2) To determine the in vitro stability of 14C-PMPA in plasma and in intestinal and liver homogenates from dog and human

Note: Tenofovir=PMPA

STUDY DESIGN: Stability of PMPA (GS-1278) was evaluated in rat, dog, and human tissues. The following cofactors were added: 500µM nicotinamide adenine dinucleotide phosphate (NADP), 5mM glucose-6-phosphate (G-6-P), 5 mM magnesium chloride, 4mM nicotinamide and 1 U/mL G-6-P dehydrogenase. The final microsomal and S9 protein concentrations were 5 mg/mL for human and 2 mg/mL for rat. Cofactors were replaced with 50 mM sodium/potassium phosphate buffer for liver homogenate studies (without cofactors). The potential formation of covalently bound adducts was also assessed by determining the association of radioactivity with protein.

In vitro metabolism of 14C-PMPA was determined in liver microsomes from control rats or following induction with [redacted] (an inducer of cytochrome P450 isozymes 1A and 2B). For rats, n>1 but exact number is not specified.

[redacted]

RESULTS:

<u>In vitro stability of PMPA in Rat Liver Microsomes (RLM)</u>

14C-PMPA was stable in rat liver homogenates with or without the addition of cofactors following incubation up to 60 min at 37°C. Recoveries were between 90-117%. Results are summarized in Table 1. There were no additional peaks observed in the radiochromatograms, therefore, no metabolites were detected. There were no differences between normal and [redacted] induced rat liver microsomes with or without cofactors.

Isomerization of PMPA was also evaluated. The relative abundance of the S-isomer remained constant throughout the study. No metabolites were detected using the chiral assay, nor were there differences in relative abundance of isomer between normal and [redacted] induced rat liver microsomes with or without cofactors. Additionally, there were no significant differences in stability of 14C-PMPA in heat-treated or untreated microsomes.

Table 1. In-vitro stability of 14C-PMPA in rat liver microsomes (control and heat-inactivated)

Reaction mixture	Incubation times 0 min		30 min		60 min	
	% PMPA remaining	% S-isomer	% PMPA remaining	% S-isomer	% PMPA remaining	% S-isomer
No Cofactors						
Saline control RLM	100	8.14	90.6	7.75	117	6.67
	100	**9.83**	**98.3**	**8.82**	**96.6**	**9.18**
[redacted] induced RLM	100	7.62	93.6	6.58	93	9.05
	100	**7.51**	**99.3**	**7.4**	**100.5**	**7.86**
With Cofactors						
Saline control RLM	100	9.38	93	7.51	110.7	5.56
	100	**5.19**	**104.9**	**9.86**	**110.5**	**6.02**
[redacted] induced RLM	100	6.8	103.6	6.97	99.1	9.15
	100	**7.61**	**100.5**	**7.77**	**102.4**	**6.55**

Bolded values refer to heat-inactivated RLM.

Stability and esterase activity in dog and human tissues

In dog and human plasma, intestinal homogenate, and liver homogenates (with cofactors), there was no detectable loss of 14C-PMPA in all reaction mixtures following 60 min of incubation and no metabolites were detected. Esterase activities were detected in plasma and homogenates, with plasma having the least amount of esterase activity. Intestinal homogenates had less activity than liver. Results are summarized in Table 2.

Table 2. In vitro stability and esterase activity of 14C-PMPA in dog and human tissues

Species	Plasma	Intestine	Liver
Dog			
% PMPA remaining	98	110	92
Esterase activity (U/mL)	7.8	12.2	43
Protein concentration (mg/mL)	ND	11.1	23.8
[redacted]			

CONCLUSIONS:

Due to the lack of metabolites detected in rat microsomal preparations and in dog and human intestinal and liver homogenates, PMPA is metabolically stable.

Effect of tenofovir and tenofovir DF on the activities of the cytochrome P-450 isoforms in human hepatic microsomes (#V990172-104)
Volume 2.061

OBJECTIVE(S): The primary objective of this study was to evaluate the metabolic effects of tenofovir and its oral prodrug, tenofovir disoproxil fumarate on CYP1A, 2C9, 2D6 2E1 and 3A4 in human hepatic microsomes.

STUDY DESIGN: Activities of CYP isoforms were determined by examining the metabolism of specific probe substrates. Table 1 lists the substrates and concentrations used:

Table 1. Probe substrates used for characterization of CYP isoform activities for CYP1A, 2C9, 2D6 2E1 and 3A4 of human hepatic microsomes

CYP isoform	Probe substrate	Concentration (μM)	Catalyzed reaction	Product
3A4	Terfenadine	100	Hydroxylation	4-hydroxyterfenadine
2D6	Dextromethorphan	80	O-demethylation	dextrorphan
2C9	Tolbutamide	50	Hydroxylation	4-hydroxytolbuatmide
2E1	Chlorzoxazone	400	Hydroxylation	6-hydroxychloroxazone
1A	7-ethoxycoumarin	200	O-deethylation	7-hydroxycoumarin

RESULTS: Substrate metabolism was measured in the absence and presence of 100 uM of tenofovir and tenofovir DF. Concentrations of 100 uM of tenofovir and tenofovir DF were chosen by the applicant because this represents approximately 300-fold higher concentrations of tenofovir observed in clinical trials. With high concentrations, however, inhibition potential may be misrepresented. Results are summarized in Table 2.

Table 2. Rates of probe substrate metabolism by human hepatic microsomes in the absence and presence of 100 μM tenofovir and tenofovir DF.

CYP Enzyme	Incubation time (min)	N	Control (nmol/mg/min)	Tenofovir (nmol/mg/min)	Tenofovir DF (nmol/mg/min)
3A4	40	4	0.018 (0.009)	0.016 (0.009)	0.018 (0.010)
2D6	20	4	0.066 (0.041)	0.064 (0.043)	0.065 (0.045)
2C9	30	3	0.218 (0.093)	0.216 (0.096)	0.209 (0.105)
2E1	20	4	1.48 (0.58)	1.5 (0.65)	1.42 (0.77)
1A	20	4	0.481 (0.182)	0.487 (0.19)	0.45 (0.180)*

*Significant compared to control ($p < 0.05$) using a paired student t-test

The rates of probe metabolism were unchanged with 100 uM of tenofovir. There was a statistically significant decrease (6.5%) in the rate of O-deethylation of 7-ethoxycoumarin with tenofovir DF. Metabolic rates of all other probes were not affected by the prodrug.

Additionally, known CYP3A4 and CYP2D6 inhibitors, ketoconazole (5 uM) and quinidine (10 uM), were used for comparison. Ketoconazole and quinidine resulted in 61% and 78% reductions in metabolic activity. These are comparable to the magnitudes of inhibition reported in the literature for ketoconazole and quinidine.

CONCLUSIONS: Tenofovir 100 uM had no effect on CYP1A, 2C9, 2D6, 2E1 and 3A4 activity in vitro. Tenofovir DF 100 uM did not affect the activity of 2C9, 2D6, 2E1 and 3A4 activity. CYP1A activity was decreased (6.5%) by the presence of tenofovir DF. The clinical relevance of this decrease, however, is minimal because tenofovir DF is rapidly cleaved by esterases to yield tenofovir. Tenofovir concentrations in clinical trials are a fraction of these tested concentrations and, consequently, may misrepresent drug interaction potential in vivo.

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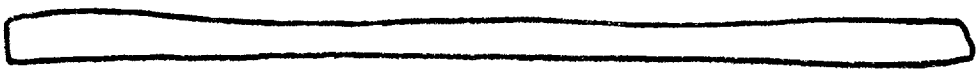
In vitro epithelial transport of tenofovir disoproxil (Bis-POC PMPA) in Cloned Caco-2 monolayers (01-VIT-4331-001.1)

OBJECTIVE: The objective of this study was to evaluate the epithelial permeability of tenofovir disoproxil, mono-POC PMPA (monoester derivative of tenofovir) and tenofovir in vitro using TC7 (a sub-clone of the Caco-2 cell line) cell monolayers.

STUDY DESIGN: This intestinal absorption study was conducted using 3 test compounds that were evaluated against 2 reference compounds in TC7 intestinal epithelial monolayers. Apical (A) to basolateral (B) permeation was determined during the 2-hour study.

SAMPLE COLLECTION: Samples were taken at 30, 60 and 120 minutes from the B (receiver) chamber and at 0 and 120 minutes from the A (donor) chamber.



RESULTS: Mean concentrations of tenofovir DF, mono-POC PMPA and tenofovir from the three studies are summarized in Table 1. No tenofovir was detected in the receiver chamber. Small amounts of mono-POC PMPA (0.01μM) were detected in the receiver chamber at 120 minutes. In the tenofovir DF study, tenofovir was not detected in the receiver chamber but both tenofovir DF and mono-POC PMPA were detected.

Table 1. Mean concentrations (uM) of tenofovir, mono-POC PMPA and tenofovir DF from individual permeability studies in the receiver chamber

Study Compound	Analyte	Time (Minutes)		
		30	60	120
Tenofovir	Tenofovir	<LOD	<LOD	<LOD
Mono-POC PMPA	Mono-POC PMPA	<LOD	<LOD	0.01 μM
Tenofovir DF	Tenofovir DF	0.01 μM	0.02 μM	0.04 μM (± 0.01 SD)
	Mono-POC PMPA	0.01 μM	0.01 μM	0.03 μM
	Tenofovir	<LOD	<LOD	<LOD

<LOD = below limit of detection

Permeability coefficients (P_{app}) for tenofovir, mono-POC PMPA and tenofovir DF and two reference compounds were determined (Table 2). The permeability of mono-POC PMPA (0.07×10^{-6} cm/sec) is 10-fold lower than tenofovir DF. Tenofovir P_{app} was not calculated because concentrations were below the limit of detection. P_{app} of reference compounds were typical of their classification.

Table 2. Permeability results for tenofovir DF, mono-POC PMPA, tenofovir and reference compounds, assayed for TC7 permeability in the apical to basolateral direction (50 uM), following a 2-hour incubation at

37 C.

Compound	Permeability Coefficient (10^{-6} cm/sec)				
	1st Determination	2nd Determination	3rd Determination	Mean	SD
Tenofovir DF*	0.69	0.72	0.59	**0.67**	0.07
Mono-POC PMPA	0.08	0.06	0.06	**0.07**	0.01
Tenofovir	<LOD	<LOD	<LOD	N/A	N/A
Propranolol#	24.25	27.04	23.62	**24.97**	1.82
Ranitidine'	2.66	2.55	0.74	**1.98**	1.08

* The permeability of tenofovir DF is expressed as the permeability of tenofovir DF equivalent, including both tenofovir DF and mono-POC PMPA
\# High permeability compound
' Low permeability compound
<LOD Below limit of detection
N/A Not applicable

In Table 3, mono-POC PMPA is in the donor phase and the receiver phase. Tenofovir is not seen in either chamber. Tenofovir DF is, therefore, most likely to be metabolized after transport across the TC7 monolayers, during the incubation.

Table 3. Mean recovery of tenofovir disoproxil and metabolites from apical and basolateral chambers, following in vitro permeability testing of tenofovir DF in TC7 monolayers (n=3)

Time (min.)	Donor [Apical Chamber] (μmole)			Receiver [Basolateral Chamber] (μmole)		
	Tenofovir Disoproxil	Mono-POC PMPA	Tenofovir	Tenofovir Disoproxil	Mono-POC PMPA	Tenofovir
0	33.52	8.41	0	0	0	0
30	ND	ND	ND	0.01	0.01	0
60	ND	ND	ND	0.02	0.01	0
120	31.43	9.88	0	0.04	0.03	0

ND = Not determined

CONCLUSIONS: The Biopharmaceutics Classification System (BCS) permeability classification for tenofovir DF, tenofovir and mono-POC PMPA is low permeability.

Protein binding of cidofovir, cyclic HPMPC, PMEA and PMPA in human plasma and serum (Report #95-DDM-XXXX-001)
Volume 2.061

OBJECTIVE(S): The primary objective of this study was to determine the human plasma and serum protein binding of cidofovir, cyclic HPMPC, PMEA and PMPA. This review will focus on PMPA only.

STUDY DESIGN: Radiolabeled [2, 8-3H] PMPA was used to determine free and bound concentrations. Total final concentrations of PMPA used were 0.01, 0.51, 5.01 10.01 and 25.01 ug/mL at 0.223 uCi/mL. These concentrations are within the range observed in clinical trials.

RESULTS:

Table 1. Protein binding of PMPA in human plasma and serum at concentrations of 0.01, 0.51, 5.01 10.01 and 25.01 ug/mL

Concentration (ug/mL)	% unbound in plasma	% unbound in serum
Mean (SD)	99.3 (3.3)	92.8 (3.6)

CONCLUSIONS: PMPA demonstrated low protein binding in human plasma and serum between concentrations of 0.01-25.01 ug/mL.

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Assessment of the safety, tolerance, pharmacokinetics and antiviral activity of intravenous tenofovir in HIV-infected patients (Study GS-96-701) Volume 2.051

OBJECTIVES: The study objectives were to investigate the safety, tolerance, pharmacokinetics and antiviral activity of intravenous tenofovir in the treatment of HIV

SUBJECTS: A total of 20 (17 M, 3 F) HIV-1 infected patients enrolled.

DESIGN: This was a randomized, double-blind, placebo-controlled study. Ten patients with HIV infection enrolled in each of the following treatment arms (4:1 for study drug:placebo):
Treatment A: 1.0 mg/kg x 1 on Day 1, then 1.0 mg/kg qd from Days 7-14
Treatment B: 3.0 mg/kg x 1 on Day 1, then 3.0 mg/kg qd from Days 7-14

A total of 16 subjects received tenofovir. For each dose cohort, eight patients received a single intravenous infusion of tenofovir and two received saline placebo, infused over 1 hour. Following a one-week washout period, the same patients received seven daily doses of intravenous tenofovir (1.0 or 3.0 mg/kg/day) or placebo by infusion.

FORMULATIONS: Intravenous tenofovir 75 mg/mL was provided by Gilead Sciences Inc. in 5 mL vials as a sterile liquid (Lot number H601).

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were obtained at predose, 0.5 (mid-infusion), 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours following drug administration on Days 1 and Day 14. Urine samples were also collected on Days 1 and 14 during time intervals of 0-4, 4-8, 8-12, 12-24, 24-48 and 48-72 hours following the dose.

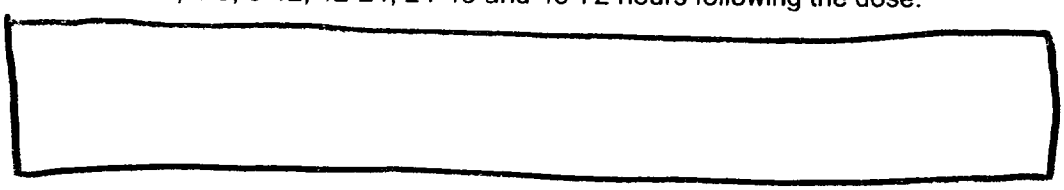


Table 1. Assay performance for the determination of tenofovir in human serum and urine

	Serum	Urine
Calibration curve range	[redacted]	[redacted]
Limit of quantitation	25 ng/mL	1 µg/mL
QC concentrations	75, 300, 750 ng/mL	3, 7.5, 15 µg/mL
QC precision (%CV)	3.5, 3.9, 5.9	4.4, 3.5, 3.0
QC bias (% nominal)	96.7, 94.8, 98.2	99.3, 99.1, 100.2

PHARMACOKINETIC ANALYSIS: Pharmacokinetic (PK) parameters for tenofovir were determined using non-compartmental methods. For Day 14 data analysis, steady-state was assumed and the dosing interval of 24 hours was also included. Wilcoxon Rank-Sum tests were performed to compare PK parameters between dose groups for each day and between days within each dose group.

PHARMACOKINETIC RESULTS:

Mean pharmacokinetic parameters of tenofovir in serum and urine are summarized in Table 2. Figures 1 and 2 illustrate mean concentration time curves for single (Day 1) and multiple (Day 14) doses of intravenous tenofovir.

Table 2: Mean pharmacokinetic parameters (± SD) for tenofovir in serum and urine following administration of tenofovir 1.0 mg/kg and 3.0 mg/kg on Days 1 and 14

Study Day and Dose	C_{max} (µg/mL)	AUC* (µg *h/mL)	T_{max} (h)	$T_{1/2}$ (h)	CLcr (mL/hr/kg)	CLr (mL/hr/kg)	% dose in urine**	CL (mL/hr/kg)
Day 1								
1.0 mg/kg	2.71 (0.87)	4.41 (0.89)	1.12 (0.17)	5.27 (0.95)	75.3 (20.5)	161 (59)	67.1(15.8)	236 (54.3)
3.0 mg/kg	8.52 (2.53)	15.2 (6.28)	0.97 (0.09)	7.80 (1.10)	78.6 (18.9)	194 (89)	84.1 (14.1)	229 (91.4)
Day 14								
1.0 mg/kg	2.50 (0.52)	4.65 (1.05)	1.05 (0.06)	7.72 (2.12)	73.2 (20.9)	164 (58)	72.3 (14.5)	227 (60.5)
3.0 mg/kg	9.55 (1.97)	20.5 (8.79)	1.01 (0.03)	8.77 (1.68)	70.5 (17.3)	123 (52)	78.4 (10.7)	168 (59.4)

* For Day 1, AUC=AUC $_{0-\infty}$
For Day 14, AUC=AUC $_{0-T}$

** For Day 1, over 72 hours
For Day 14, over 24 hours

Figure 1. Mean concentration time curves of tenofovir 1.0 mg/kg on Days 1 and 14

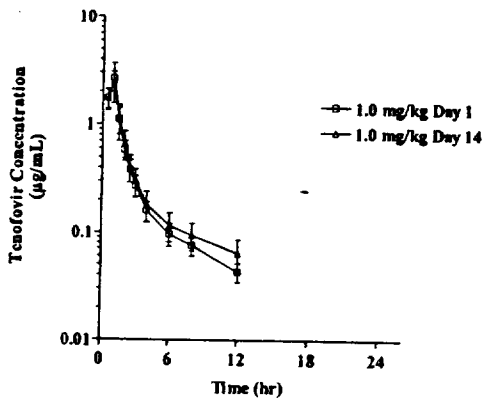
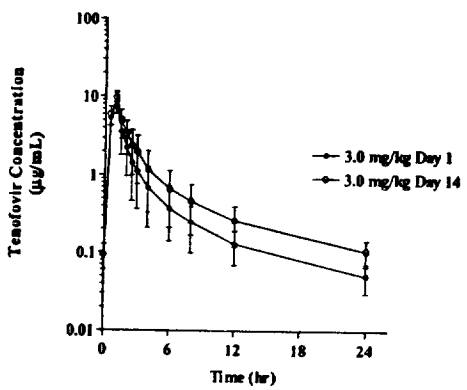


Figure 2. Mean concentration time curves of tenofovir 3.0 mg/kg on Day 1 and Day 14



With nonparametric analysis of pharmacokinetic parameters following single-doses of tenofovir (Wilcoxon Rank-Sum Test), there were no significant differences between dose groups in CL, CLr values or dose-normalized values of Cmax, AUC. Terminal half life was longer in the 3.0 mg/kg dose group compared to those who received 1.0 mg/kg (7.8 hr vs. 5.3 hr). The terminal half-life of the 1.0 mg/kg dose was most likely underestimated because serum concentrations reached levels close to the LOQ.

The terminal half-life of tenofovir was prolonged on Day 14 versus Day 1 in the 1.0 mg/kg dose group (7.7 hr vs. 5.3hr). On Day 14, volume of distribution was significantly larger than on Day 1 (1250± 549 mL/kg vs. 759 ± 326 mL/kg). This may be due to problems in estimating T1/2 or measuring low concentrations of tenofovir. Multiple-doses of 1.0 mg/kg did not affect other PK parameters. Accumulation was not observed in this dose group.

In the 3.0 mg/kg dose group, C_{max} and Vss were unchanged with repeated dosing. The terminal half-life was, however, slightly prolonged on Day 14 compared to Day 1 (8.77 hr vs. 7.8 hr). AUC, CL and CLr values were significantly affected by multiple dosing of 3.0 mg/kg. Tenofovir AUC was significantly greater on Day 14 (20.5± 8.8 µg*h/mL) than on Day 1 (15.2± 6.28 µg *h/mL). Tenofovir clearance values were significantly less on Day 14 than on Day 1 with a mean decrease of 27%. Renal clearance of tenofovir was also significantly lower on Day 14 than on Day 1. C_{last} on Day 14 was higher compared to Day 1 (0.11 vs. 0.05µg/mL), indicating possible accumulation with multiple doses of 3.0 mg/kg, but this is not more than what is expected.

Overall mean renal clearance of tenofovir was consistently greater than baseline creatinine clearance values. In both dose groups, renal clearance of tenofovir exceeded the glomerular filtration rate indicating active tubular secretion contributes to the renal elimination of tenofovir.

CONCLUSIONS: The conclusions of this study are as follows:

1. Clearance decreased with multiple doses of 3.0 mg/kg and terminal half-life was prolonged following single and multiple doses in both dose groups. As postulated by the sponsor, concentrations being close to the LOQ of the assay may have contributed to the underestimation of the terminal half-life and other PK parameters. Saturation of renal elimination, however, may have also been possible at the higher dose of tenofovir.

2. The mean renal clearance of tenofovir exceeded creatinine clearance, indicating net tubular secretion.

3. Urinary recovery was approximately 70-80% of total dose over 72 hours of urine collection.

4. Tenofovir C_{max} was dose proportional but the increase in AUC was greater than dose proportional with multiple doses of tenofovir 3.0 mg/kg compared to 1.0 mg/kg. Given the decrease in renal clearance, saturable renal elimination may occur at higher multiple doses of tenofovir.

Dose ranging study of the safety, tolerance, pharmacokinetics and antiviral activity tenofovir DF (TDF) in HIV-infected patients (Study GS-97-901) Volume 2.052

OBJECTIVES: The study objectives were to investigate the safety, tolerance, pharmacokinetics and antiviral activity of tenofovir DF in the treatment of HIV

SUBJECTS: A total of 46 (41 M, 5 F) HIV-1 infected patients enrolled.

DESIGN: This was a Phase I/II, double-blind, placebo-controlled, dose-ranging, single- and multiple-dose study. Subjects were randomized into the following cohorts (7-12 patients/cohort):

Cohort 1: TDF 75 mg qd
Cohort 2: TDF 75 mg qd + hydroxyurea 500 mg bid
Cohort 3: TDF 150 mg qd
Cohort 4: TDF 300 mg qd
Cohort 5: TDF 600 mg qd

Note: Subjects were allowed to enter an extended dosing phase of TDF 300 mg qd. Also, the rationale for studying hydroxyurea with 75 mg of tenofovir DF is not indicated in the protocol or study report. It is assumed that the rationale for evaluating tenofovir DF + hydroxyurea is the same as the rationale for the coadministration of hydroxyurea + ddI. When administered with hydroxyurea, HIV activity of ddI was increased. The applicant is not pursuing the combination of tenofovir DF + hydroxyurea at this time.

Subjects received TDF under fasted conditions on Day 1. Following a 1-week washout period, subjects received twenty-eight once-daily doses of TDF under fed conditions. For the fed portion of the study, subjects received a standardized, high-fat breakfast (~700 kcal, 40% fat) on PK days (Day 8, 15 and 35). On non-PK days, subjects were instructed to consume a routine breakfast prior to their TDF dose.

FORMULATIONS: Tenofovir DF 75 mg white oral tablets (and matching placebo) were formulated at [redacted] and provided by Gilead Sciences, Inc. Lot numbers for TDF tablets: I702. Lot number for placebo tablets: I701.

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were obtained over 24 hours post-dose following the single oral dose of TDF in the fasted state (Day 1), the first dose in the fed state (Day 8) and after eight once-daily doses in the fed state (Day 15). Samples were obtained at predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 48 hours (if applicable) following drug administration. Additional blood samples were obtained at 48 hours post dose following the last dose on Day 35 for the 300 mg, 600 mg and 75 mg + HU dose groups. Urine samples were collected during time intervals of 0-4, 4-8, 8-12, 12-24 hours. For Day 1, additional urine samples were collected at 24-48 and 48-72 hours following the dose.

[redacted]

PHARMACOKINETIC ANALYSIS: Pharmacokinetic parameters were determined using noncompartmental methods and the log/linear trapezoidal rule for area-under-the-curve.

PK parameters evaluated are: AUC, Cmax, Tmax, T1/2 and CL/F. Rank ANOVA with Fisher's least significant difference tests was performed on pharmacokinetic parameters to assess dose proportionality. Signed Rank tests were performed to evaluate food-effect (Day 8 Fed to Day 1 Fasted) and to assess changes in PK parameters over time (Days 8 vs. 15 vs. 35) in each dose group.

PHARMACOKINETIC RESULTS: Mean pharmacokinetic parameters of tenofovir are summarized in Table 2. Figure 1 presents steady-state tenofovir serum concentration time curves for the 75 mg, 150, 300 and 600 mg dose groups on Days 8 and 15. There is limited evaluation of the pharmacokinetics of tenofovir DF 75 mg, 75 mg± hydroxyurea and 150 mg due to concentrations being below the LOQ of the assay.

C_{max} and AUC values appear to be dose proportional over the range of tenofovir DF 75 mg to 600 mg. The oral bioavailability of tenofovir DF was enhanced by 39% and 34% for the 300 and 600 mg group under fed conditions (high-fat breakfast). Median C_{max} was not altered significantly but Tmax was prolonged to 1.2 h from 0.8 h.

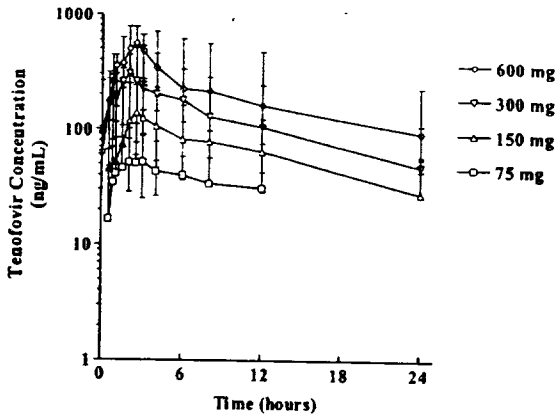
Table 2: Mean pharmacokinetic parameters (± SD) for tenofovir in serum and urine following administration of tenofovir DF 75 mg, 75 mg + hydroxyurea (HU), 150 mg, 300 mg and 600 mg single- and multiple-dose (once daily).

Note: Day 1= Fasted; Days 8, 15, 35=Fed
There was a 7-day washout between Days 1 and 8

Dose and Study Day	C_{max} (ng/mL)	AUC* (ng*h/mL)	C_{last} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	CLcr (mL/hr/kg)	CLr (mL/hr/kg)	% dose in urine	CL/F (mL/hr/kg)
TDF 75 mg									
Day 1	68.6**	-	25.4**	0.8**	-	86 (16)	-	16 (9)	-
Day 8	68.2 (25.7)	365 (183)	21.5 (10.1)	1.8 (0.7)	-	82 (15)	-	27 (4)	-
Day 15	69.2 (19.4)	562 (261)	25.2 (10.7)	2.2 (1.1)	-	86 (15)	-	30 (10)	354**
TDF 75 mg + HU									
Day 1	71.2**	71**	30.5**	0.5**	-	107 (18)	-	19 (9)	-
Day 8	54.2**	199**	26.4**	0.9**	-	102 (12)	-	16 (7)	-
Day 15	63.4**	-	31.6**	0.8**	-	112 (19)	-	25 (11)	-
Day 35	58.6**	-	32.2**	1.5**	-	111 (17)	-	27 (8)	-
TDF 150 mg									
Day 1	143.5 (71.1)	476 (251)	31.6 (4.7)	1.0 (0.5)	-	87 (17)	-	20 (9)	-
Day 8	148 (67.8)	896 (643)	38.5 (7.3)	2.4 (1.4)	-	88 (13)	-	23 (8)	-
Day 15	180.9 (69.1)	1572 (700)	38.7 (14.6)	2.1 (1.0)	12**	88 (18)	160**	29 (11)	555**
TDF 300 mg									
Day 1	294.4 (137.2)	2093**	34.3 (7)	1.1 (0.7)	11.9**	94 (19)	203**	19 (6)	910**
Day 8	362 (100.5)	3185 (866)	41.3 (12.4)	2.1 (1)	13 (4)	94 (11)	173 (65)	21 (6)	614 (176)
Day 15	325.5 (119.1)	3324 (1370)	64.4 (25.4)	2.7 (0.8)	12.9 (2.1)	99 (20)	183 (60)	32 (10)	588 (166)
Day 35	319 (108)	3299 (1070)	31.2 (4)	2.3 (1)	14.3 (1.1)	87 (27)	-	-	589 (171)
TDF 600 mg									
Day 1	611.5 (274.8)	3372**	61.7 (44.9)	0.9 (0.3)	13**	92 (23)	-	-	1083**
Day 8	611.8 (232.5)	5028 (1528)	62.7 (20.9)	1.4 (0.3)	12.7 (2.5)	96 (28)	121 (54)	13 (3)	734 (230)
Day 15	640.7 (191.9)	6068 (2468)	111.3 (53.2)	2.3 (0.8)	12.3 (1.5)	87 (22)	95 (42)	16 (3)	632 (191)
Day 35	550.8 (200.9)	5971 (2917)	53.1 (34.3)	2.2 (1)	15.3 (1.1)	92 (18)	104 (55)	17 (6)	631 (188)

* For the 75 mg and 150 mg cohorts, AUC=AUC $_{0\text{-last}}$
For Days 1 and 8, AUC=AUC $_{0\text{-}\infty}$
For Days 15 and 35, AUC=AUC $_{0\text{-}T}$
** Median values
\- Not calculated due to missing data

Figure 1. Mean concentration-time profiles of tenofovir in serum following administration of tenofovir DF 75 mg, 150 mg, 300 mg and 600 mg (with food)



Oral bioavailability of tenofovir DF relative to intravenous tenofovir (from Study 701)

Bioavailability of the 300 mg and 600 mg doses of TDF was determined by comparing $AUC_{0-\infty}$ (dose-normalized) on Day 1 to the PK of intravenous tenofovir. Mean AUC following 1.0 mg/kg of intravenous tenofovir was 4410 ng*h/mL. Estimated oral bioavailabilities of tenofovir DF 300mg and 600 mg administered in the fasted state were 25 and 21%, respectively.

CONCLUSIONS

1. Tenofovir pharmacokinetics were dose proportional across the dose range of 75 mg to 600 mg of tenofovir DF.
2. Approximate bioavailabilities following a single of 300 mg and 600 mg of tenofovir DF in the fasted state were 25 and 21% (median values). Because bioavailability was determined using two different studies (Study 701 and Study 901), these values are only estimates and may not reflect true bioavailability.
3. The oral bioavailability of tenofovir DF was enhanced by 39% and 34% for the 300 and 600 mg group under fed conditions (high-fat breakfast). Median C_{max} was not altered significantly but T_{max} was prolonged to 1.2 h from 0.8 h. PK data from only five subjects were available for assessment and may, therefore, not accurately evaluate the food effect in this study. Another study, GS-00-914, evaluates the food effect with a more appropriate study design and the intended commercial formulation.
4. Steady-state PK parameters of tenofovir are unchanged compared to single dosePK parameters.
5. Renal function was not altered following multiple doses of tenofovir DF.

Phase III study of the safety and efficacy of tenofovir disoproxil fumarate (TDF) in combination with other antiretroviral agents in HIV-1 infected patients (Study GS-99-907) Volume 2.055

BACKGROUND: Prior to this study, long term pharmacokinetics of tenofovir DF in HIV-infected individuals were not evaluated. In this study report, the applicant submitted PK data of tenofovir from a subset of subjects over the first 24 weeks of treatment with TDF.

OBJECTIVES: The study objectives were to determine the safety, efficacy and long term pharmacokinetics of TDF over 24 and 48 weeks of treatment with TDF in combination with other antiretrovirals.

SUBJECTS: A total of 552 HIV-infected subjects enrolled. Fourteen male (n=10) and female (n=4) subjects enrolled for the pharmacokinetic portion of the study. Nine of these subjects (6 M, 3 F) provided pharmacokinetic data for tenofovir.

DESIGN: This was a Phase III, double-blind, placebo-controlled, multi-center pharmacokinetic substudy. Subjects were randomized to receive either TDF 300 mg orally once daily or placebo.

FORMULATIONS: Film-coated tenofovir DF 300 mg oral tablets [redacted] and matching placebo tablets were formulated at [redacted] and provided by Gilead Sciences, Inc. Lot numbers for TDF tablets: J001B1, J904D, J909F1 and J909F2. Lot number for placebo tablets: J908D. The intended commercial formulation was used.

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were obtained at predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours following drug administration. Following the dose on Day 1 only, an additional blood sample was obtained at 24 hours. Urine samples were collected over 24 hours following the first oral dose of TDF then over 12 hours at week 12 and 24 during time intervals of 0-4, 4-8, 8-12 and 12-24 hours (if necessary).

[redacted]

PHARMACOKINETIC ANALYSIS: Signed ranked tests were performed on pharmacokinetic parameters (AUC, Cmax, Tmax, T1/2, CL/F) to compare single-dose vs. steady-state pharmacokinetics. PK parameters were determined using noncompartmental methods. Analysis of variance (ANOVA) was performed, as appropriate.

PHARMACOKINETIC RESULTS: Mean pharmacokinetic parameters of tenofovir are summarized in Table 1. Cmax increased from 282 ng/mL (Day 1) to 349 ng/mL (Week 12.) but by Week 24, decreased to 256 ng/mL with less variability. AUC values at Day 1

were comparable to Week 12 but declined by Week 24, T_{max} was generally unchanged. Because of the large variability in these parameters (and small sample size), detection of any statistical significance is limited.

Creatinine clearance was unchanged from Days 1 through Week 24 (CLcr=97 mL/kg/min at Day1, 93 at Week 12 and 91 at Week 24). Tenofovir clearance slightly increased at Week 24 compared to Days 1 and Week 12 (773 vs 680 and 660 mL/kg/min). This finding was not significant.

Table 1: Mean pharmacokinetic parameters (± SD) for tenofovir in serum following administration of tenofovir DF 300 mg once daily at Day 1, Week 12 and Week 24

		C_{max} (ng/mL)	AUC* (ng*h/mL)	C_{min} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	CLcr (mL/hr/kg)	CL/F (mL/hr/kg)
Day 1	N=9	282 (139.2)	2929 (750)	46.2 (21.5)	2.4 (0.8)	12.1 (2.6)	97 (19)	660 (242)
Week 12	N=7	348.6 (121)	2968 (1156)	66.5 (37.6)	2.1 (0.8)	18.7 (13.5)	93 (19)	680 (322)
Week 24	N=7	256 (77)	2341 (491)	36.9 (16.8)	2.6 (1.0)	14.4 (4.6)	91 (21)	773 (270)

* For Day 1, AUC=$AUC_{0-\infty}$
For Weeks 12 and 24, AUC=AUC_{0-24}

CONCLUSIONS

The small sample size of this pharmacokinetic substudy and the intersubject variability observed in these PK parameters likely limited the ability to detect significant differences in the pharmacokinetic data. According to the results of this study, the conclusions for the study are:

1. There was minimal change and decreased variability of PK parameters of tenofovir over 24 weeks of therapy. Steady-state pharmacokinetics of tenofovir appeared to be consistent with PK parameters from Study 901.

2. Renal function did not appear to be altered over time.

3. Although clearance of tenofovir slightly increased by Week 24, this was not a significant change compared to the first dose. As mentioned previously, these data are inconclusive because of the small sample size.

Assessment of the pharmacokinetics of tenofovir disoproxil fumarate (TDF), lamivudine (3TC), didanosine (ddI), indinavir (IDV), lopinavir/ritonavir (LPV/RTV) and efavirenz (EFV) in healthy volunteers (Study GS-00-909). Volume 2.056

OBJECTIVES: The study objectives were:

1) to determine the pharmacokinetics of TDF, 3TC, ddI, IDV, LPV/RTV and EFV when administered alone;
2) to determine the pharmacokinetic parameters of TDF in combination with 3TC, ddI, IDV, LPV/RTV and EFV;
3) to evaluate whether the pharmacokinetic parameters of either drug are affected following co-administration of TDF with 3TC, ddI, IDV, ABT-378/RTV and EFV in healthy subjects

SUBJECTS: A total of 103 male and female healthy volunteers enrolled. Ninety-three of these subjects were evaluable.

DESIGN: This was a Phase I, open-label, multiple-dose, crossover, drug interaction study. Subjects in each cohort were randomized to receive the following treatments in a random sequence:

Cohort 1 (n=15): TDF 300 mg qd x 7 days, TDF 300 mg + 3TC 150 mg bid x 7 days, 3TC 150 mg bid x 7 days; 7-day washout between treatments
Cohort 2 (n=18): TDF 300 mg qd x 7 days, TDF 300 mg + ddI 250mg (wt < 60 kg) or 400 mg (wt > 60 kg) qd x 7 days, ddI 250mg (wt < 60 kg) or 400 mg (wt > 60 kg) qd x 7days; 7-day washout between treatments
Cohort 3 (n=15): TDF 300 mg qd x 7 days, TDF 300 mg + IDV 800 mg tid x 7 days, IDV 800 mg tid x 7 days; 7-washout between treatments
Cohort 4 (n=24): TDF 300 mg qd x 7 days, TDF 300 mg + LPV/RTV 400 mg/100 mg bid x 14 days, LPV/RTV 400 mg/100 mg bid x 14 days; 21-day washout for TDF + LPV/RTV and LPV/RTV treatments; 7-day washout for TDF alone
Cohort 5 (n=31): TDF 300 mg qd x 7 days, TDF 300 mg + EFV 600 mg qd x 14 days, EFV 600 mg qd x 14 days; 28-day washout for TDF + EFV and EFV treatments; 7-day washout for TDF alone

Treatments in Cohorts 1-3 and 5 were administered under fasted conditions. Treatments in Cohort 4 were administered under fed conditions (high-fat meal). For Cohort 2, TDF was administered 1 hour following ddI. Both TDF and ddI were administered under fasted conditions.

Note: IDV and ddI are administered on an empty stomach whereas tenofovir DF is usually administered following a meal for enhanced bioavailability. In clinical practice, patients will take these drugs at different times of the day. Therefore, results from Cohorts 2 and 3 may not be exactly reflective of the drug interactions between tenofovir DF and ddI and IDV that will occur clinically.

FORMULATIONS: The intended commercial formulation of tenofovir DF 300 mg oral tablets ([redacted] Lot# J905D1, were supplied by Gilead Sciences, Inc. Commercially available oral formulations of lamivudine, didanosine (buffered tablets), indinavir, lopinavir/ritonavir and efaverinz were used.

[redacted]

Table 1. Assay performance for the determination of tenofovir in human serum

	Tenofovir
Calibration curve range	[redacted]
Limit of quantitation	2.99 ng/mL
QC concentrations, ng/mL	8.98, 239.56, 449.17
QC precision (%CV)	10.1, 8.4, 9.5
QC bias (% nominal)	96.5, 99.7, 98.3

Validated methods were used for determining 3TC, ddI, IDV, LPV, RTV and EFV.

SAMPLE COLLECTION: Blood and urine samples were obtained over a 24-hour period on Day 7 except for LPV/RTV, TDF + LPV/RTV, EFV and TDF + EFV treatment groups (Day 14). For all treatment groups, blood samples were collected at predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours following their respective doses. For Cohort 2, TDF was administered 1 hour following ddI. Urine samples were collected at 0-4, 4-8, 8-12 and 12-24 hours.

PHARMACOKINETIC ANALYSIS: Pharmacokinetic parameters (C_{max}, T_{max}, C_{last}, C_{min}, AUC, CL/F and T1/2) were determined using non-compartmental analysis. A general linear model with subject within sequence, sequence, treatment and period as factors was applied. Drug interactions were not considered significant if 90%CI values for least-squares mean AUC and C_{max} ratios for the drug in combination to the drug alone fell within 80-125% limits.

PHARMACOKINETIC RESULTS:

Effect of lamivudine, didanosine, indinavir, lopinavir/ritonavir and efavirenz on tenofovir pharmacokinetics

Mean pharmacokinetic parameters of tenofovir are summarized in Table 1. Figures 1a to 1e illustrate mean concentration-time curves of tenofovir comparing tenofovir alone and tenofovir with the co-administered drug. The PK parameters of tenofovir (and %CV values) do not appear to be affected by the concomitant administration of 3TC, ddI or EFV. The 90%CI values for C_{max} and AUC for tenofovir were within acceptable limits (80-125%).

Tenofovir C_{max} values were slightly increased with IDV (379 ng/mL) versus when given alone (323 ng/mL) with 90%CI of 96.9-132.9%. AUC values, however, remained comparable (90%CI=95.4-119.0%). T_{max} of tenofovir was also unchanged for TDF + IDV (1.22 hr) vs. TDF alone (0.87). Because the increase in C_{max} of tenofovir is small and AUC is unchanged, this is not likely a clinically significant drug interaction. Other PK parameters of tenofovir were unchanged with IDV co-administration.

With LPV/RTV, the C_{max} and AUC values of tenofovir were significantly increased by 31% (90%CI=112-153%) and 34% (90%CI=125-144%), respectively. Tenofovir DF (or tenofovir) does not undergo CYP metabolism, therefore, the interaction is unlikely to be caused by inhibition of metabolism. This may be due to a food effect of tenofovir DF with concomitant LPV/RTV since subjects were not advised to take tenofovir DF with food when taken alone. These tenofovir concentrations have also been observed in

previous clinical trials (901 and 914), and, therefore, the available data suggest these concentrations are generally safe. Long term data are unavailable at this time. There is, however, a safety concern that there may be a larger increase in tenofovir concentrations for patients taking higher doses of ritonavir with tenofovir DF.

Table 2: Comparison of mean pharmacokinetic parameters (SD) for tenofovir in serum when administered tenofovir DF alone and with interacting drugs (lamivudine, didanosine, indinavir, lopinavir/ritonavir and efaverinz)

	C_{max} (ng/mL)	AUC (ng*h/mL)	C_{min} (ng/mL)*	T_{max} (h)	$T_{1/2}$ (h)	CL/F (mL/hr/kg)
TDF alone	379.70 (97.97)	2651.85 (502.58)	58.06 (14.72)	0.81 (0.27)	16.66 (4.6)	803.09 (174.04)
TDF+3TC	388.02 (103.17)	2581.75 (661.94)	54.02 (18.41)	0.82 (0.20)	16.65 (4.14)	844.71 (219.12)
90%CI	**95.9-108.0**	**84.7-108.4**	**72.8-112.1**			
TDF alone	320.24 (75.49)	2351.02 (687.3)	50.9 (16.3)	1.18 (0.77)	21.56 (18.48)	939.99 (283.29)
TDF+DDI	321.95 (98.27)	2264.24 (805.50)	47.7 (18.3)	0.84 (0.25)	14.69 (2.98)	1009.9 (374.91)
90%CI	**86.3-112**	**85.8-102.3**	**79.4-103.7**			
TDF alone	322.54 (110.21)	2288.34 (629.22)	47.0 (13.0)	0.87 (0.33)	15.23 (2.61)	831.2 (193.23)
TDF+IDV	379 (118.63)	2493.27 (750.82)	50.3 (16.6)	1.22 (0.42)	15.21 (2.6)	782.57 (247.73)
90%CI	**96.9-132.9**	**95.4-119**	**91.5-120.8**			
TDF alone	297.95 (99.83)	2462.54 (826.72)	52.6 (25.5)	2.29 (0.83)	15.02 (7.62)	887.28 (263.84)
TDF+LPV/RTV	389.93 (134.46)	3225.93 (921.63)	68.2 (24.8)	2.32 (1.48)	15.34 (8.97)	660.63 (182.24)
90%CI	**112.1-153**	**124.8-144.2**	**110.7-147.5**			
TDF alone	299.48 (84.81)	2378.47 (588.08)	49.8 (15.2)	0.98 (0.68)	15.67 (4.82)	832.01 (269.08)
TDF+EFV	321.52 (92.77)	2333.65 (477.35)	50.0 (17.1)	1.1 (0.62)	15.3 (2.97)	823.25 (173.95)
90%CI	**94.4-121.5**	**92.2-105.6**	**90.2-110.5**			

*90%CI for C_{min} values used untransformed parameters; $C_{min}=C_{tau}$

Figure 1a-e: Mean concentration-time curves for tenofovir when administered TDF alone vs. TDF + co-administered drug

Figure 1.a. TDF alone vs. TDF+3TC

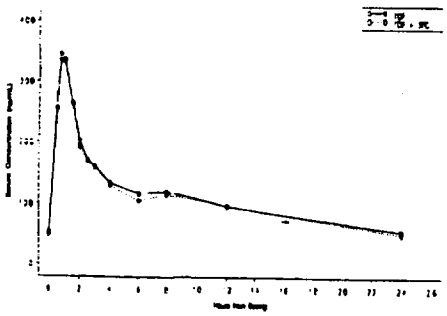


Figure 1.b. TDF alone vs. TDF+ddI

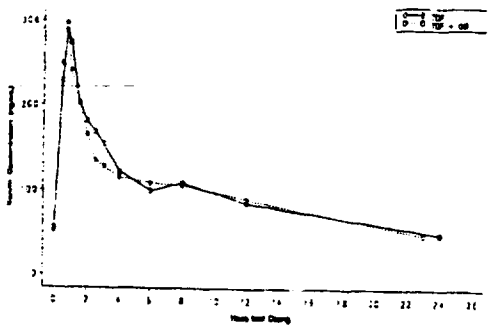


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Figure 1.c. TDF alone vs. TDF +IDV

Figure 1.d. TDF alone vs. TDF+ LPV/RTV

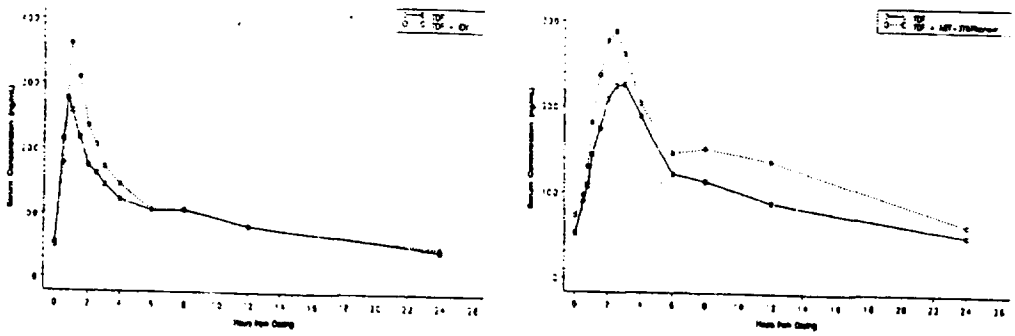
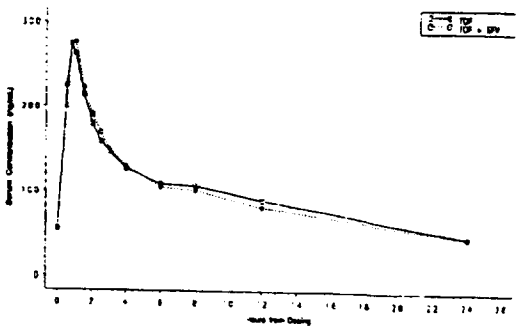


Figure 1.e. TDF alone vs. TDF +EFV



Effect of tenofovir on the pharmacokinetics of lamivudine, didanosine, indinavir, lopinavir/ritonavir and efaverinz

Mean PK parameters of coadministered are summarized in Table 2. Figures 2a to 2f illustrate the comparison of mean concentration-time curves of these agents when given alone versus concomitantly with tenofovir.

C_{max} values of 3TC were decreased when given with tenofovir. Least-squares mean ratios for 3TC in combination with TDF was 76.2% (90%CI=66.3-87.6%) for C_{max} and 97.3% (90%CI=82.3-115%) for AUC. Overall exposure of 3TC did not appear to change, however, a decrease in 3TC C_{max} was observed. Because the mechanism of action of 3TC is intracellular and the total exposure of 3TC did not change with TDF, the efficacy of 3TC is most likely unaffected by this decrease in C_{max}. Dosage adjustments are not recommended at this time.

ddI C_{max} and AUC values were significantly increased by 28% (90%CI=111.2-148%) and 44% (90%CI=131-158.8%), respectively, when administered with tenofovir. Figure 3a and 3b illustrate the effects of individual values for ddI C_{max} and AUC for subjects receiving tenofovir DF + ddI vs. ddI alone. This interaction may be caused by these drugs competing for the same renal elimination pathways. There was no increase in the incidence of ddI-associated AEs (pancreatitis, neuropathy, paresthesias, elevations in serum amylase and lipase) observed in this study or pooled clinical studies.

When tenofovir DF was administered with IDV, there was an 11% decrease in IDV C_{max}.

This decrease is minimal and will not likely affect efficacy of IDV. Other IDV PK parameters were unchanged and comparable in variability.

Both C_{max} and AUC values of LPV were decreased by approximately 15% with concomitant administration of tenofovir DF. C_{min} values of LPV were similar. The decreases observed in LPV C_{max} and AUC may be attributed to lower RTV concentrations. Concomitant administration of tenofovir with LPV/RTV decreased C_{max} and AUC values of RTV by 28% and 24%. It is postulated that tenofovir DF may decrease the bioavailability of RTV but the mechanism for this is unknown. Figure 4a, 4b and 4c illustrate the individual changes in LPV C_{max}, AUC and C_{min} for subjects receiving tenofovir DF + LPV/RTV vs. LPV/RTV alone. Although PK parameters tended to decrease, the magnitude of these decreases were not enough to warrant a dosage adjustment of LPV/RTV.

EFV PK parameters were unchanged with concomitant administration of tenofovir.

Table 3: Comparison of mean pharmacokinetic parameters (SD) and 90%CI of mean ratios for lamivudine, didanosine, indinavir, lopinavir/ritonavir and efaverinz in plasma when administered alone and with tenofovir DF

	C_{max} (ng/mL)	AUC (ng*h/mL)	C_{min} (ng/mL)*	T_{max} (h)	$T_{1/2}$ (h)	CL/F (mL/hr/kg)
3TC alone	2166 (861)	8594.28 (2753.88)	73 (27)	0.72 (0.21)	7.18 (1.8)	771.98 (2026.28)
3TC+TDF	1497 (532)	7600.58 (2396.82)	85 (29)	1.66 (0.67)	7.7 (1.73)	427.14 (525.33)
90%CI	**66.3-87.6**	**82.3-115**	**107.8-122.3**			
DDI alone	2131 (871)	3539.86 (1304.19)	0	0.62 (0.15)	1.39 (0.28)	1684.02 (609.74)
DDI+TDF	2761 (1107)	5167 (1848.62)	0	0.82 (0.23)	1.44 (0.26)	1161.53 (454.25)
90%CI	**111.2-147.8**	**131.1-158.8**	-			
IDV alone	9460 (2605)	27526.16 (10655.98)	288 (254)	0.99 (0.34)	1.13 (0.25)	428.32 (139.36)
IDV+TDF	8935 (3531)	37364.87 (12496)	328 (302)	1.42 (0.87)	1.2 (0.41)	457.95 (186.31)
90%CI	**70.3-111.7**	**82.2-110.1**	**95.6-128.6**			
LPV/RTV alone						
LPV component	12778.9 (2463.3)	116691.1 (21812.7)	7839.7 (2004.2)	3.82 (2.1)	12.6 (5.79)	52.5 (12.02)
RTV component	1160.2 (517.6)	6591.32 (2374.15)	281.8 (118.6)	3.92 (2.16)	5.14 (5.36)	259.79 (117.99)
LPV/RTV+TDF						
LPV component	11037.3 (3141)	101758.07 (32007.01)	7243.4 (2783.3)	3.82 (3.15)	13.84 (6.52)	64.34 (22.93)
RTV component	889.3 (523.5)	5193.86 (2566.23)	296.6 (240.8)	4.08 (2.67)	5.41 (2.05)	353.61 (174.21)
90%CI (LPV)	**76.8-93.6**	**77.8-92.8**	**85.3-103.4**			
90%CI (RTV)	**56.8-90.8**	**66.4-86.9**	**77.7-137.0**			
EFV alone	3.844 (1.368)	54.84 (17.48)	1.57 (0.57)	3.39 (1.24)	28.03 (17.74)	164.61 (58.38)
EFV+TDF	3.67 (1.178)	52.6 (17)	1.51 (0.55)	3.46 (1.23)	28.17 (22.26)	172.25 (60.72)
90%CI	**90.8-101.8**	**92.9-99.5**	**93.8-99.4**			

*90%CI for C_{min} values used untransformed parameters; $C_{min}=C_{tau}$

Figures 2a-f: Mean concentration time curves of coadministered drugs when administered alone vs. coadministered drug +TDF

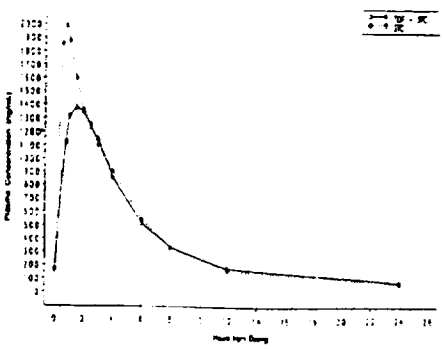


Figure 2.a. 3TC alone vs. TDF+3TC alone vs. TDF+ddI

Figure 2.b. ddI

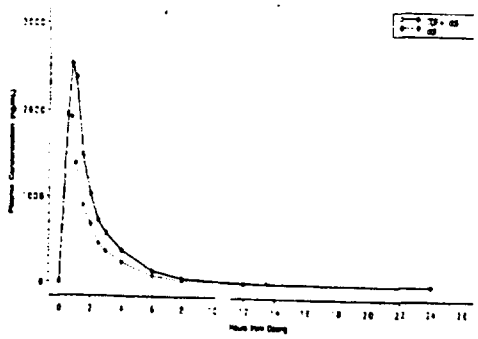
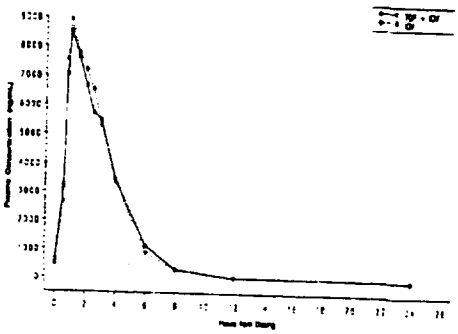


Figure 2.c. IDV alone or TDF+IDV

Figure 2.d. LPV/RTV alone or TDF+ LPV/RTV (LPV concentrations)



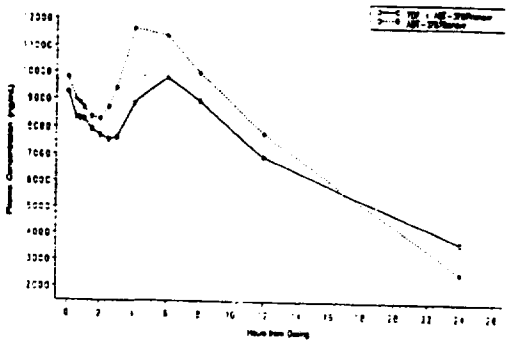
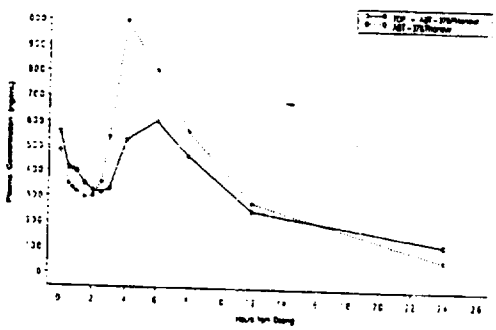
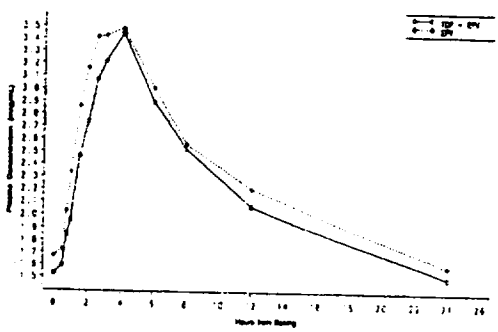


Figure 2.e. LPV/RTV vs. TDF+LPV/RTV (RTV component)

Figure 2.f. EFV vs. TDF + EFV





Figures 3a + b: Comparison of individual Cmax and AUC values of ddI in subjects receiving tenofovir DF (Treatment B) + ddI vs. ddI alone (Treatment C)

Figure 3a:

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Figures 4a, b and c: Comparison of individual Cmax, AUC and Cmin values of LPV in subjects receiving tenofovir DF + LPV/RTV (Treatment B) vs. LPV/RTV alone (Treatment C)

Figure 4a:

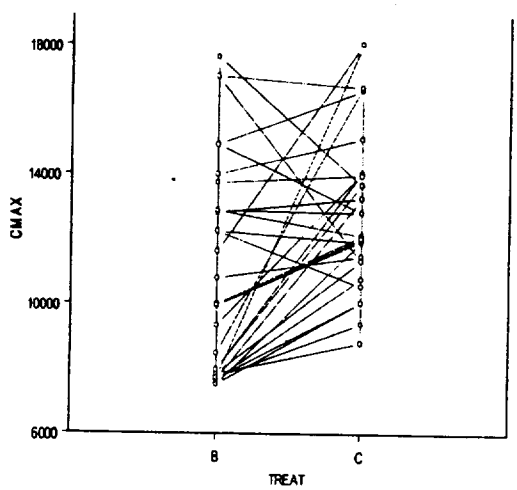


Figure 4b:

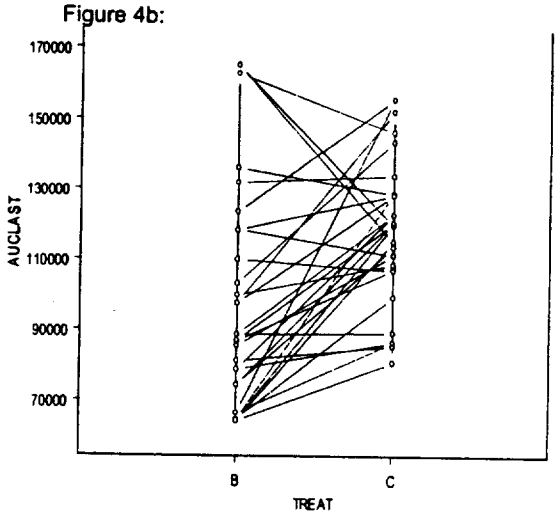
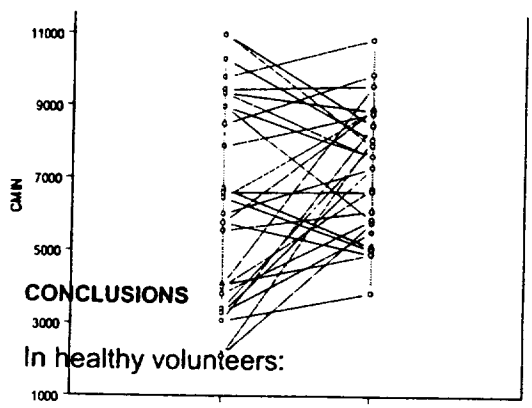


Figure 4c:



CONCLUSIONS

In healthy volunteers:

1) Tenofovir pharmacokinetic parameters were not affected by the concomitant administration of lamivudine, didanosine or efaverinz.
2) . Increases in tenofovir C_{max} and AUC with concominant administration with indinavir

or lopinavir/ritonavir are comparable to concentrations deemed safe in clinical trials. There is, however, a safety concern that there may be a larger increase in tenofovir concentrations for patients taking higher doses of ritonavir with tenofovir DF. Another drug interaction study with LPV/RTV is recommended to determine the drug interaction potential between tenofovir DF and LPV/RTV underfed conditions, as appropriate.

3) A significant drug interaction was observed with didanosine + tenofovir DF in which Cmax and AUC values of didanosine increased by 28% and 44%. A renal interaction is most likely the mechanism of this interaction. Although the applicant did not observe ddI-specific AEs in pooled studies, patients should be warned of this possible drug interaction and potential for AEs that may be associated with ddI.
4) LPV/RTV C_{max} and AUC values decreased for both components when administered with TDF. Since the decreases are 15% for LPV, dosage adjustment is not warranted at this time.
5) Efaverinz PK parameters were not affected by tenofovir DF.

Bioequivalence of the clinical and intended commercial formulation of tenofovir disoproxil fumarate (TDF) **and** the effect of food on the bioavailability and pharmacokinetics of the intended commercial formulation of tenofovir disoproxil fumarate (Study GS-00-914).
Volume 2.059

OBJECTIVES: The study objectives were:

4) To determine the pharmacokinetic profiles of a single 300 mg dose of the clinical formulation of TDF (4 x 75 mg tablets) under fasted conditions and a single 300 mg dose of the intended commercial formulation of TDF (1 x 300 mg tablet) under fasted and fed conditions;
5) To evaluate the bioequivalence of the 300 mg clinical dose and intended commercial tablets under fasted conditions;
6) To evaluate the effect of food on the bioavailability of the intended commercial formulation of TDF

SUBJECTS: A total of 40 male and female healthy volunteers enrolled. Thirty-nine of these subjects (20 males; 19 females) provided pharmacokinetic data.

DESIGN: This was a Phase I, integrated, open-label, single-dose, 3-way crossover, bioequivalence and food effect study. Subjects were randomized to receive the following treatments for Periods 1, 2 and 3:

Treatment A: 4 x 75 mg TDF clinical formulation (reference) under fasted conditions
Treatment B: 1 x 300 mg TDF intended commercial formulation (test) under fasted conditions
Treatment C: 1 x 300 mg TDF intended commercial formulation (test) under fed conditions*

Study duration was 18 days with 7-day washouts between visits.

*Note: Standard high-fat breakfast was administered.

FORMULATIONS: The intended commercial formulation of tenofovir DF 300 mg oral tablets [redacted] Lot #J905D1, and the clinical formulation of tenofovir DF 75 mg oral tablets (white, round-shaped), Lot # J802A, were supplied by Gilead Sciences, Inc. Batch sizes [redacted]

PHARMACOKINETIC SAMPLE COLLECTION: Blood samples were obtained at predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36 and 48 hours following drug administration. Urine samples were collected during time intervals of –1-4, 4-8, 8-12, 12-24, 24-36, 36-48 hours.

[redacted]

	Serum	Urine
Calibration curve range	[redacted]	
Limit of quantitation	3.01 ng/mL	0.501 µg/mL
QC concentrations	3.01, 8.97, 239.33, 448.75 ng/mL	0.501, 1.504, 30.074, 80.198 µg/mL
QC precision (%CV)	6.6, 6.4, 6.8	5.3, 4.0, 6.5
QC bias (% nominal)	100.1, 103.3, 98.2	99.3, 104.1, 105.9

PHARMACOKINETIC ANALYSIS: Pharmacokinetic parameters (AUC_{0-24}, $AUC_{0-\infty}$, Cmax, Tmax, Kel, T1/2, CL/F and % dose recovered in the urine) were determined using noncompartmental methods and the log-linear trapezoidal rule in WinNonlin. Parameters were analyzed using analysis of variance (ANOVA) appropriate for the crossover design. Bioequivalence and food effect were evaluated by 90% confidence intervals (two-sided) on the ratio of mean for AUC and Cmax. 90%CI within 80-125% limits for AUC and Cmax were deemed bioequivalent. The original protocol used 70-143% for Cmax but this review will consider the most updated 90%CI limits for bioequivalence (80-125% for both AUC and Cmax).

PHARMACOKINETIC RESULTS: Mean pharmacokinetic parameters (SD), 90% CI values and % mean ratios are summarized in Table 2. Figure 1 illustrates mean concentration time curves of single 300 mg doses of tenofovir DF clinical formulation and intended commercial formulation in the fasted state and the intended commercial formulation in the fed state.

Effect of formulation on the bioequivalence of tenofovir DF 75 mg and 300 mg tablet

Because 90% CI values for AUC and C_{max} were within 80-125% limits (95.8-105.8%; 87.8-105.6%), the two formulations are considered bioequivalent. T_{max} is similar between formulations

Effect of food on the PK parameters of the intended commercial formulation of tenofovir DF 300 mg tablets

Consumption of a high-fat breakfast prior to the administration of tenofovir DF 300 mg resulted in a significant increase in bioavailabilty. Geometric mean AUC and Cmax values were approximately 40% and 14% higher under fed conditions. Tmax was also delayed by one hour, resulting in Tmax at 2 hours. 90%CI value for AUC was 131.5-145.1%, indicating a food effect with tenofovir DF. The 90%CI for Cmax was within 80-125%.

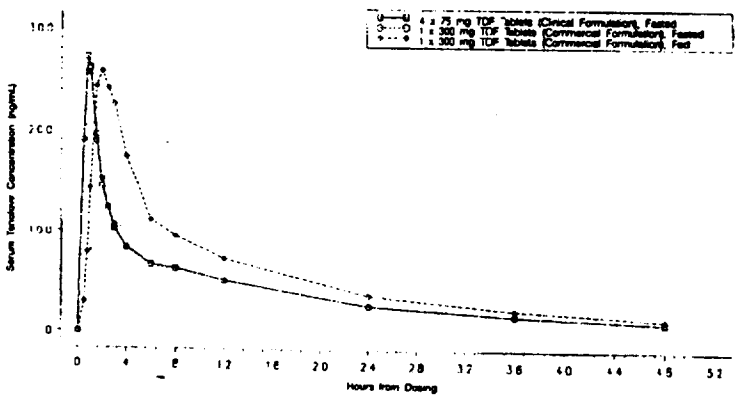
Table 2: Mean pharmacokinetic parameters (± SD), 90%CI values and % mean ratios for tenofovir in Treatment A vs. B (Effect of formulation) and Treatment B vs. C (Effect of Food)

	C_{max} (ng/mL)	AUC (ng*h/mL)	T_{max} (h)	% dose recovered in	CLr (mL/hr/kg)

				urine	
Effect of Formulation:					
Treatment A (ref) vs. B (test)					
Clinical formulation 4 x 75 mg tablets (fasted)	307 (89)	2266 (550)	1.01 (0.60)	16.9 (4.9)	172.5 (67)
Commercial formulation 1 x 300 mg tablet (fasted)	296 (90)	2287 (685)	0.99 (0.38)	16.7 (4.8)	167.3 (43.8)
90%CI	**87.8-105.6**	**95.8-105.8**			
% mean ratio	**96.3**	**100.7**			
Effect of Food:					
Treatment B (ref) vs. C (test)					
Commercial formulation 1 x 300 mg TDF (fasted)	296 (90)	2287 (685)	0.99 (0.38)	16.7(4.8)	167.3 (43.8)
Commercial formulation 1 x 300 mg TDF (fed)	334 (80)	3100 (598)	2.03 (0.88)	23.5 (4.9)	168.6 (41.1)
90%CI	**104.4-125.4**	**131.5-145.1**			
% mean ratio	**114.4**	**138.2**			

Following single dose administration of the clinical and intended commercial formulations, the percent of tenofovir recovered in the urine was 16.9% and 16.7%, respectively. In the fed state, % dose recovered in urine increased to 23.5 %. This increase is most likely due to the increased bioavailability.

Figure 1. Mean concentration-time curves of 300 mg (4 x 75 mg tablets) tenofovir DF clinical formulation under fasted conditions, 300 mg (1 x 300 mg tablet) intended commercial formulation under fasted conditions and 300 mg (1 x 300 mg tablet) intended commercial formulation under fed conditions



CONCLUSIONS

1. The intended commercial formulation of tenofovir DF (1 x 300 mg tablet) is bioequivalent to the clinical formulation (4 x 75 mg tablet).

2. Ingestion of a high-fat meal results in an increase in Cmax and AUC by 14% and 38% following single-dose administration of the intended commercial formulation of tenofovir DF 300 mg.

DISSOLUTION METHOD

6 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.